nature reviews endocrinology

https://doi.org/10.1038/s41574-024-00970-4

Review article

Check for updates

Endocrine and cellular physiology and pathology of the insulin-like growth factor acid-labile subunit

Robert C. Baxter

Abstract

The acid-labile subunit (ALS) of the insulin-like growth factor (IGF) binding protein (IGFBP) complex, encoded in humans by *IGFALS*, has a vital role in regulating the endocrine transport and bioavailability of IGF-1 and IGF-2. Accordingly, ALS has a considerable influence on postnatal growth and metabolism. ALS is a leucine-rich glycoprotein that forms high-affinity ternary complexes with IGFBP-3 or IGFBP-5 when they are occupied by either IGF-1 or IGF-2. These complexes constitute a stable reservoir of circulating IGFs, blocking the potentially hypoglycaemic activity of unbound IGFs. ALS is primarily synthesized by hepatocytes and its expression is lower in non-hepatic tissues. ALS synthesis is strongly induced by growth hormone and suppressed by IL-1β, thus potentially serving as a marker of growth hormone secretion and/or activity and of inflammation. *IGFALS* mutations in humans and *Igfals* deletion in mice cause modest growth retardation and pubertal delay, accompanied by decreased osteogenesis and enhanced adipogenesis. In hepatocellular carcinoma, *IGFALS* is described as a tumour suppressor; however, its contribution to other cancers is not well delineated. This Review addresses the endocrine physiology and pathology of ALS, discusses the latest cell and proteomic studies that suggest emerging cellular roles for ALS and outlines its involvement in other disease states.

Sections

University of Sydney, Kolling Institute, Royal North Shore Hospital, St Leonards, New South Wales, Australia.
e-mail: robert.baxter@sydney.edu.au

Key points

- The insulin-like growth factor (IGF) acid-labile subunit (ALS), encoded by *IGFALS*, forms a circulating ternary complex with IGF binding protein (IGFBP)-3 or IGFBP-5, and IGF-1 or IGF-2.
- This ternary complex acts as a reservoir of IGF-1 and IGF-2 in the bloodstream and has a central role in regulating their endocrine transport and tissue bioavailability.
- Owing to the induction of its expression by growth hormone and suppression by IL-1β, ALS might serve as a marker of growth hormone secretion and/or activity and of inflammation.
- Mutation, deletion or inactivation of the gene that encodes ALS in humans and mice decreases circulating levels of IGF-1 and IGFBP-3, causing moderate growth deficiency and abnormalities in bone and carbohydrate metabolism.
- As a marker of inflammation and sepsis, ALS levels are low in critical illness, cardiovascular disease and COVID-19; in some conditions, ALS levels might predict disease progression and mortality.

Introduction

Among the multiple binary complexes that can form between the six insulin-like growth factor (IGF) binding proteins (IGFBP-1 to IGFBP-6) and either IGF-1 or IGF-2, only those containing IGFBP-3 or IGFBP-5 can combine with a third protein termed the acid-labile subunit (ALS; encoded by *IGFALS*) to form ternary complexes. These ternary complexes, which are regulated by growth hormone (GH), have a central role in the endocrine transport and bioavailability of IGF-1 and IGF-2. As a result of this functionality, ALS has a major influence on postnatal growth and metabolism.

In the 1960s, IGF bioactivity (originally called nonsuppressible insulin-like activity or somatomedin) was discovered in fractions corresponding to 6–10 kDa in acidified human serum fractionated by size exclusion chromatography. By contrast, this bioactivity appeared at ~150 kDa in non-acidified serum[1]. Acidification of human serum also revealed a major peak of IGF-binding activity corresponding to 50–70 kDa (refs. 2,3). Affinity crosslinking experiments suggested that the ~150 kDa form of IGF activity could be attributed to an oligomer of subunits that were 24–28 kDa (ref. 4). However, the true structure became clearer with the demonstration that a protein fraction (peak 3) isolated from human serum by anion-exchange chromatography, when combined with acid-stable IGF-binding activity and 6–10-kDa IGF activity, could reconstitute a complex of about 150 kDa, which was similar to the IGF bioactivity found in whole serum[5,6]. Peak 3 was irreversibly inactivated by acidification, leading to its description as the 'acid-labile subunit'[5].

These discoveries led to the isolation and characterization of the acid-stable binding protein, IGF binding protein 3 (IGFBP-3; initially called BP53)[7], followed by cloning of complementary DNA and determination of the primary structure[8]. Similarly, the acid-labile component, ALS, was purified and characterized[9,10], and its primary structure was determined by cloning[11]. These advances enabled the high-molecular-weight IGF complex to be reconstituted from highly purified IGFBP-3, ALS and IGF-1 or IGF-2 (ref. 12). Somatomedin or IGF activity was known to be decreased in the serum of people with GH deficiency (GHD)[13] and was restored after administration of exogenous human GH[14]. This GH dependence was also demonstrated for the acid-stable binding protein IGFBP-3 (refs. 5,15) and ALS[5,16].

This Review will discuss the endocrine physiology and pathology of ALS, as well as cell and proteomic studies that suggest emerging cellular roles for ALS. The involvement of ALS in GH disorders and other disease states will also be outlined.

Structure of ALS and the ternary complex

The complementary DNA sequence of ALS revealed that it is a member of the leucine-rich repeat (LRR) family of proteins. LRR proteins typically include multiple copies of a 20–30-amino-acid sequence rich in leucine residues, with the hallmark repeat sequence LxxLxLxxNxL in which x is any amino acid[17]. ALS contains 20 repeating units, mostly of 24 amino acids, including 6 leucines in each repeat (however, LRR19 and LRR20 each have slightly less than 24 amino acids), and 18 copies of the hallmark sequence, with occasional substitutions of leucine by other hydrophobic residues[11] (Fig. 1). LRR proteins generally adopt a solenoid or superhelical configuration, which results in a curved 'horseshoe' structure[17,18]. Initially, ALS was modelled to adopt a fully curved, toroidal structure with a negatively charged internal surface[19]. However, subsequent analysis predicted the more conventional horseshoe shape[20], confirmed in a seminal cryo-electron microscopy (cryo-EM) study as a 'flat horseshoe', when ALS was complexed with IGFBP-3 and IGF-1 (ref. 21) (Fig. 2). Human ALS is encoded by *IGFALS*, located on chromosome 16p13.3, and a phylogenetic tree including *IGFALS* orthologues from 71 species has been constructed[22]. The LRR structure is well conserved among vertebrates, with the amino acid sequence of zebrafish ALS showing >50% similarity to that of human ALS[22].

The human ALS precursor protein consists of 605 amino acids: a 27-residue signal peptide followed by the mature sequence of 578 amino acids, which has a molecular weight of 63.3 kDa (ref. 11). A total of 370 different *IGFALS* coding variants have been reported in an analysis of >60,000 exomes of people with a range of ethnicities, over 90% being missense or in-frame deletions or insertions[23]. Mature human ALS has six potential N-linked glycosylation sites, five of which (N37, N69, N341, N488 and N553, numbered excluding the signal peptide) have bound glycans as determined by cryo-EM[21] (Fig. 1). Electrophoretically, serum-derived ALS appears as an 84–86 kDa doublet, probably reflecting various glycosylation states, and can be sequentially deglycosylated to several smaller forms[24].

Early biochemical studies showed that, although IGF-1 or IGF-2 binding to IGFBP-3 is similar in the presence or absence of ALS, IGFBP-3 must be in a binary complex before its high-affinity interaction with ALS can occur[10] (Fig. 2). ALS binds to IGFBP-3–IGF-1 and IGFBP-3–IGF-2 in 1:1 molar ratio with an affinity of about 10^9 l/mol (refs. 10,21). Binding is decreased by increasing salt concentration, and is maximal at pH 4.5–5.0, but irreversibly abolished below pH 3.5 (ref. 25). It has been reported both in rat serum and *Xenopus* oocytes that ALS can form complexes with unoccupied IGFBP-3 (refs. 26,27). However, these are probably low-affinity interactions as cryo-EM analysis indicates that both IGF-1 and IGFBP-3 contribute to the surface that interacts with ALS, with IGF-1 'clamped' by both the N-terminal and C-terminal domains of IGFBP-3, and the binary complex filling most of the concave surface of the ALS horseshoe[21] (Figs. 1 and 2).

Using mutagenesis, a basic motif in the IGFBP-3 C-terminal domain (residues 228–232 of the mature protein) was shown to be required for high-affinity ALS binding[28]. However, structural studies point to IGFBP-3 residues on either side of this motif (the C-terminal α3 helical

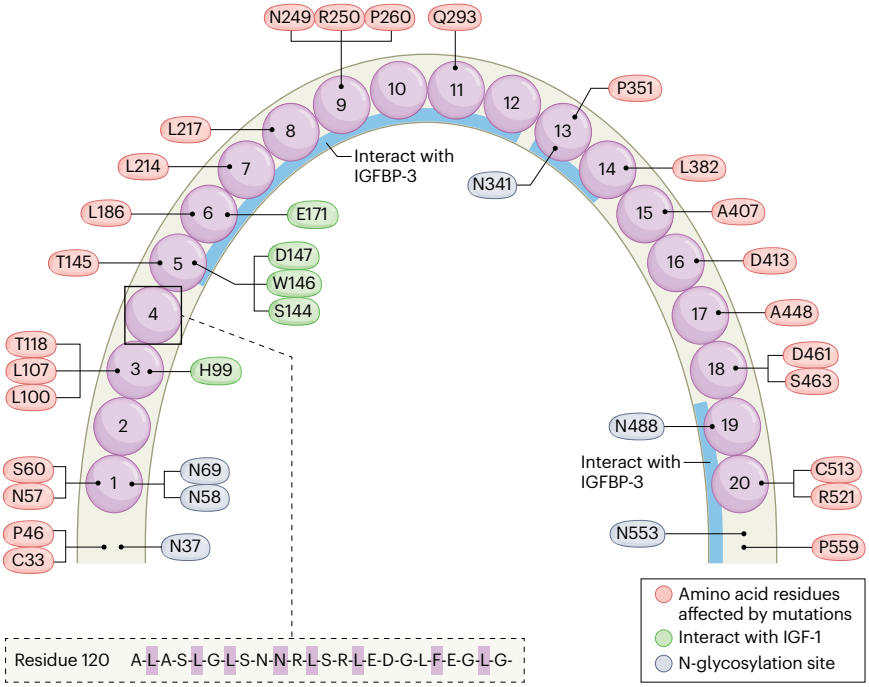

Fig. 1 | Structure of the acid-labile subunit. Representation of the mature human acid-labile subunit sequence[11] with 20 repeating leucine-rich (LRR) units from residues 48 to 521 (the last two are missing a few residues). The sequence of LRR4 is shown as an example, with repeating Leu (L), Asn (N) and Phe (F) residues highlighted. Consensus N-glycosylation sites (N-X-S/T) are indicated in grey on the concave side; all except N58 are thought to carry glycans[21]. Residues that interact with insulin-like growth factor (IGF)-1 are shown in green[21]. Regions of IGF binding protein (IGFBP)-3 interaction are broadly represented by blue arcs[21]. On the convex side, residues altered by nonsense or missense mutations, as recorded in the Human Gene Mutation Database or elsewhere[100], are shown in red. Note that numbering excludes the 27-residue signal peptide.

region and the C-terminal loop) that make direct contact with ALS in the ternary complex[21]. IGFBP-5 shows strong sequence homology with IGFBP-3 in its C-terminal domain, and IGF–IGFBP-5 binary complexes also interact with ALS through C-terminal IGFBP-5 residues[29,30], but to date there are no structural studies on this interaction. Similar to IGFBP-3, IGFBP-5 must be occupied by IGF-1 or IGF-2 to interact with ALS, and no other IGFBP is capable of binding ALS[29]. As elucidated by cryo-EM modelling, the specificity for IGFBP-3 and IGFBP-5 might be explained by structural features of IGF-1–IGFBP-3 and IGF-1–IGFBP-5 binary complexes that facilitate interaction with ALS, as well as steric barriers to ALS interaction that are present in binary complexes between IGF-1 and IGFBP-1, IGFBP-2, IGFBP-4 and IGFBP-6 (ref. 21).

Site, development and age dependence of ALS synthesis

Early in situ hybridization studies found rat ALS transcripts predominantly located in the liver. ALS transcripts were uniformly expressed by hepatocytes, but mRNA was also seen in rat kidney, where it was localized to the epithelial cells of the cortical proximal tubules[31]. By contrast, using the RNAse protection assay (which is more sensitive than in situ hybridization), bovine ALS mRNA was identified in muscle, lung, heart, small intestine, adipose and brain, as well as liver (the most abundant site)[32]. In porcine tissues, muscle, spleen and uterus showed clear expression, in addition to liver[33]. ALS mRNA has also been reported in zebrafish liver, heart, kidney and ovary[34]. Of the human tissues surveyed in The Human Protein Atlas, liver is overwhelmingly the predominant site of expression, with stomach also a notable site. ALS is identified as a matrisome protein (that is, it is associated with the extracellular matrix) in human liver[35], kidney[36] and ovary[37]. Low-level expression is also seen across a range of human brain regions in The Human Protein Atlas. Another study detected ALS in the anterior pituitary, but not in the posterior pituitary or frontal cortex[38].

Similar to IGF-1, ALS is developmentally regulated in mammals. Levels of ALS in human umbilical cord serum, measured by immunoassay, are around 1 mg/l at 25 weeks gestation, rising to 3–4 mg/l at full term[39,40] (Fig. 3a). In addition, the ratio of IGFBP-3 found in ~150 kDa ternary complexes to that in ~50 kDa binary complexes increases from about 0.5:1 to 2:1 over the same period, reflecting an increasing role for ALS in IGF transport[39]. Postnatally, mean serum levels of ALS increase steadily from around 5 mg/l at 0–2 months to about 25 mg/l in late puberty and early adulthood, then slowly decline in older adults, with a mean level in 93 healthy adults, aged 18–65 years, of approximately 24 mg/l (ref. 16) (Fig. 3a). A similar age dependence has been reported in other human studies[41,42], with a similar pattern seen in rodent serum[43–45]. Unlike IGFBP-3, for which declining serum levels in ageing adults do not reflect its increased cellular production[46], serum levels of ALS seem to mirror hepatic gene expression. The age-dependent decline might indicate 'unhealthy' ageing, as healthy centenarians have significantly higher plasma levels of ALS than people with reduced functional independence[47] (Fig. 3b).

In rat liver, ALS mRNA was extremely low at postnatal day 2 in both males and females, rising after about week 3 to plateau at weeks 6–10 (ref. 48); a similar sharp rise between embryonic day 20 and postnatal day 80 was seen by in situ hybridization[31]. Other studies also show increasing induction of ALS mRNA as hepatic development progresses, although less dramatic, with term fetal rat liver expressing 30% of the adult level[49]; a similar increase was reported in porcine liver[33]. Quantitative human *IGFALS* expression studies to parallel the pattern of regulation of serum levels of ALS through the lifespan have not been reported. However, a transcriptome-wide comparison of human liver gene expression between people aged <49 years (median: 34 years) and >74 years (median: 79 years) identified ALS as one of the most prominent age-related transcripts, as it decreased by 50% in the older group[50] (Fig. 3c).

GH and other regulatory factors

Serum levels of IGF–IGFBP-3–ALS complexes are GH-dependent in humans[4,5,16,51] and rodents[44,52,53]. Levels of the ternary complex are decreased in states of GHD or resistance and increased by over secretion of GH (such as in acromegaly) or exogenous GH administration. In humans, ALS mRNA levels in the liver, similar to IGF-1 mRNA levels, increase in response to 5 days of recombinant human GH administration. By contrast, IGFBP-3 mRNA shows no response, despite all three proteins being increased in the circulation[54]. The increase in serum levels of IGFBP-3 can be explained by its stabilization in circulating complexes with GH-dependent IGF-1 and ALS. GH also stimulates ALS mRNA expression in porcine and rat liver and hepatocyte cultures[33,55,56], which is mediated by STAT5a and STAT5b binding to the ALS promoter[57] (Fig. 4). The involvement of JAK2 in ALS regulation is evidenced by the almost complete loss of *Igfals* expression in mice with hepatocyte-specific *Jak2* deletion[58]. Cell culture studies have also revealed regulation of ALS mRNA and/or protein by insulin and IGF-1 (ref. 53) (upregulated), dexamethasone and epidermal growth factor[55], transforming growth factor-β and the somatostatin analogue octreotide[59], cAMP[60,61] and IL-1β[62,63] (all downregulated) (Fig. 4).

ALS in endocrine physiology

Although proteomic analysis has identified ALS as an extracellular matrix protein[64], ALS is currently understood to have a primarily endocrine role. ALS is predominantly synthesized in the liver (discussed in a previous section); however, catheterization studies in healthy adults have been unable to demonstrate hepatosplanchnic release of ALS[41,65]. Although the serum concentration of IGFBP-3 is approximately equimolar to the sum of IGF-1 and IGF-2 concentrations[15,66], ALS circulates in at least twofold excess[16,41]. The estimated molar excess depends on assay calibration (for example, whether calculated protein masses include glycosylation). Its circulating half-life, estimated in critically ill patients, is about 30 h (ref. 67). However, a much shorter half-life of 2 h was determined for human ALS injected into partially GH-deficient rats[68]. Human IGFBP-3, infused with IGF-1 as an intravenous bolus to healthy rats, was largely found in the ternary-complexed form within 2 min, reflecting the ready availability of excess, unoccupied ALS in the circulation[69].

Both IGF-1 and IGF-2 injected (separately) as a bolus in rats cause acute hypoglycaemia[70]. IGF–IGFBP–ALS ternary complexes form a reservoir of IGFs in the circulation, limiting IGF access to the tissues and thereby blocking their hypoglycaemic action. Thus, IGFBP-3 co-injected with IGF-1 completely reversed the hypoglycaemic effect of IGF-1 alone, whereas a mutated form of IGFBP-3 that inhibited ALS interaction (but had normal IGF binding) was unable to prevent hypoglycaemia[71]. Similarly, in human endothelial cell monolayer cultures, the addition of ALS reduced the transendothelial transport of IGF-1 complexed with either IGFBP-3 or IGFBP-5, which is consistent with the inability of the ternary complex to cross the capillary endothelium and exit the bloodstream[72]. Nevertheless, ALS and ternary complexes are found in body fluids apart from blood, for example, in human skin interstitial fluid[73], ovarian follicular fluid[74] and synovial fluid[75,76]. This finding might reflect local rather

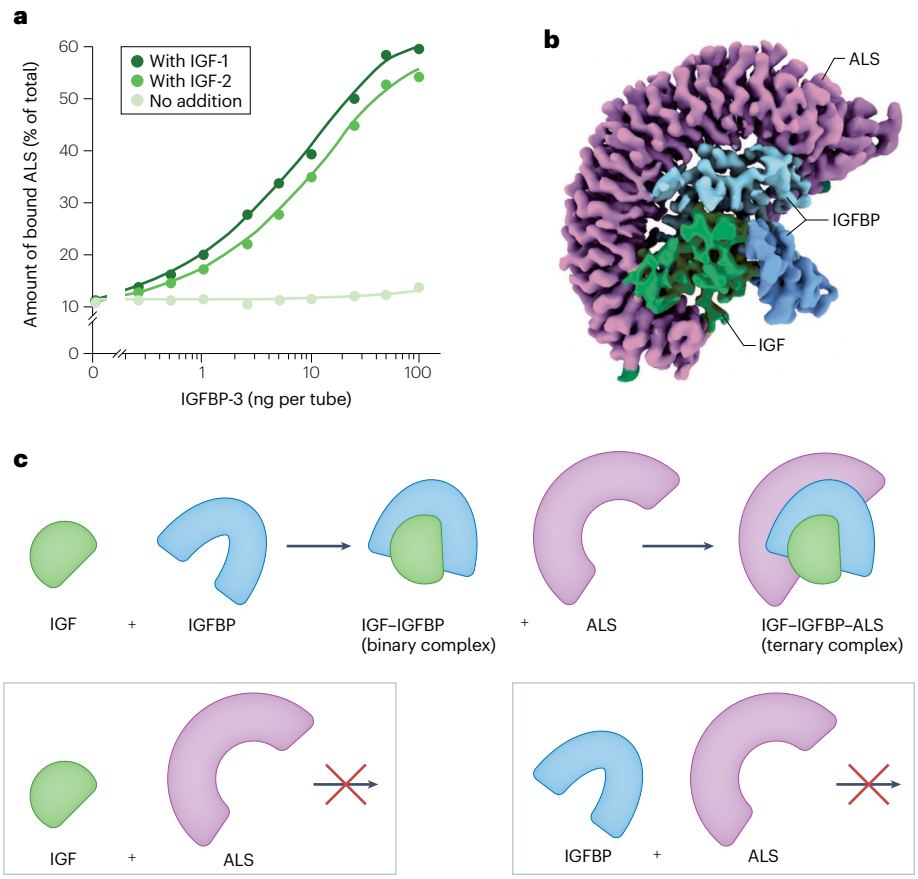

Fig. 2 | Complex formation by the acid-labile subunit. a, Binding of radiolabelled acid-labile subunit (ALS) to insulin-like growth factor (IGF) binding protein (IGFBP)-3 in the absence or presence of IGFs. Binding is essentially undetectable in the absence of IGF-1 or IGF-2. **b**, Structure of the human IGF-1–IGFBP-3–ALS complex, determined by cryogenic electron microscopy. **c**, Pictorial representation of the complex formation between IGF-1 or IGF-2, IGFBP-3 or IGFBP-5, and ALS. ALS does not bind to either IGF or IGFBP alone, but requires a binding surface formed by the IGF–IGFBP binary complex, as shown by cryogenic electron microscopy[21]. Part **a** adapted from ref. 10, CC BY 4.0. Part **b** adapted from ref. 21, CC BY 4.0.

than hepatic production, as reported for porcine and ovine ovarian tissue[32,77]. Although ALS seems to block IGFs in circulation from entering tissues, ALS is positively associated with growth rate across species. For example, the human cord serum level of ALS is a statistically significant predictor of birth length[40], ALS expression is an indicator of growth rate in molluscs[78] and hepatic *Igfals* expression is correlated with the postnatal growth rate in marsupials[79]. Interestingly, dALS (the *Drosophila* orthologue of ALS, also known as Convoluted[22]) can also exist in a ternary complex with IGF-like and IGFBP-like proteins and has a negative effect on growth, decreasing body mass when overexpressed[80]. In postnatal humans and mice, almost all studies of the relationship between ALS levels and growth relate to states of ALS deficiency, as discussed in subsequent sections.

Effects of *Igfals* deletion in mice

In the first reported mouse model of ALS deficiency, homozygous null mice showed normal prenatal survival and birthweight, and only a 13% weight reduction at 10 weeks, despite almost 90% loss of circulating levels of IGFBP-3 and no apparent compensatory increase in the serum levels of other IGFBPs[81]. Serum levels of IGF-1 were reduced to about 40% of wild-type levels (Table 1). As expression of the genes encoding IGFBP-3 and IGF-1 was not affected by *Igfals* deletion, their reduction in the circulation was attributed to increased clearance in the absence of the ternary complex. The modest growth reduction in the absence of ALS was unexpected in view of the reported association between ALS and growth rate and was taken as evidence of the importance of local rather than endocrine IGF-1 in determining growth in mice[81]. Crossing *Igfals*-null (ALSKO) mice with LID mice (null for hepatic *Igf1* expression) caused a further loss of circulating levels of IGF-1 to 15% of wild-type levels, which was accompanied by a marked elevation in levels of GH (not seen with *Igfals* deletion alone) and very little residual IGFBP-3 (ref. 82). IGF-1 clearance was calculated to be about four times faster in the ALSKO–LID mice than in control mice. However, paradoxically, serum levels of free IGF-1 were estimated to be four times higher in the ALSKO–LID mice than in control mice.

Measured at 8 weeks after birth, body weight was similar in ALSKO and ALSKO–LID mice, but body length, femur length and markers of bone development were notably lower in ALSKO–LID than in wild-type or ALSKO mice. Some of these parameters could be partially restored

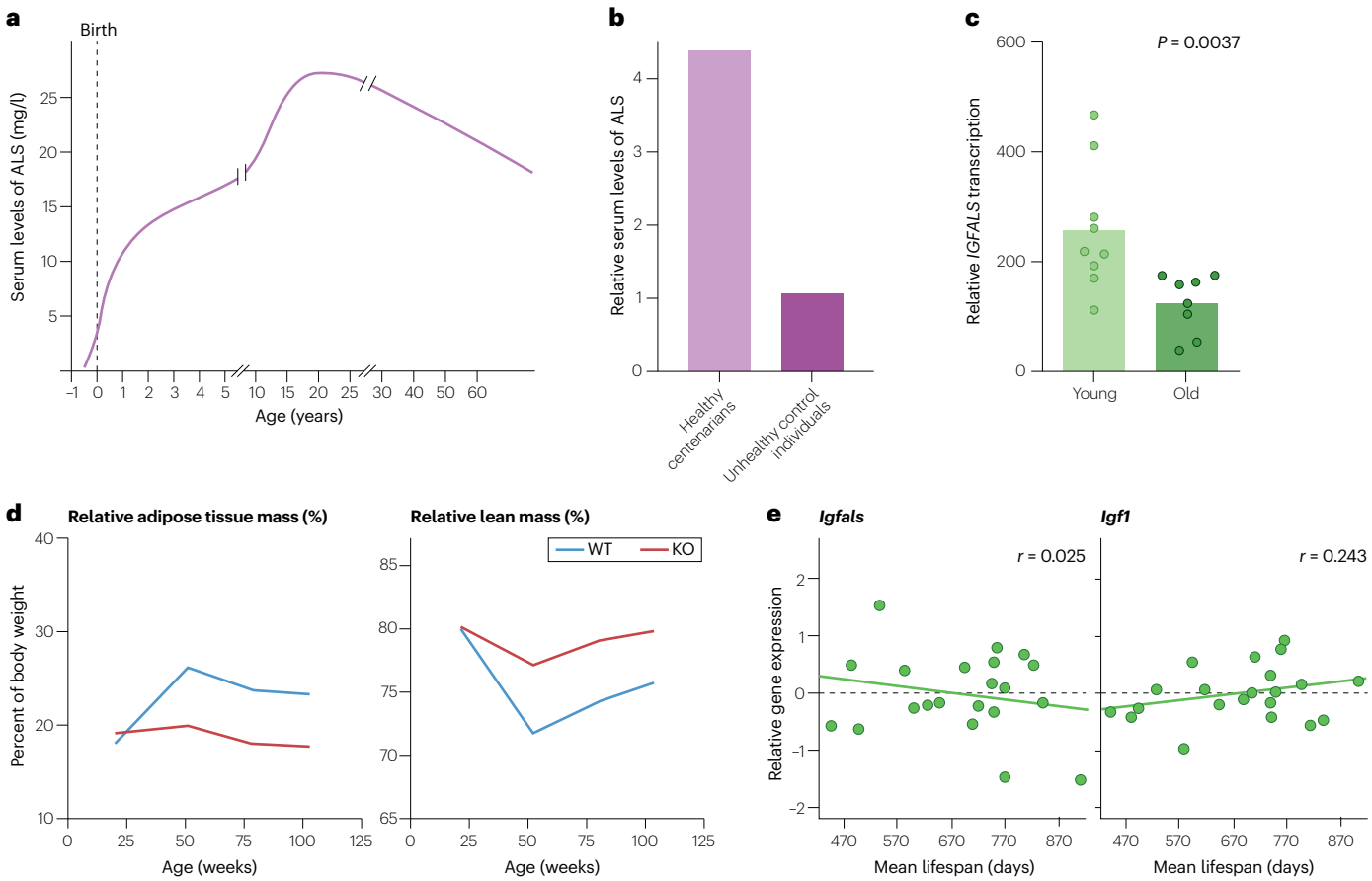

Fig. 3 | The acid-labile subunit and ageing. a, Graphical summary of serum levels of acid-labile subunit (ALS) in humans. ALS levels rise rapidly from mid-gestation and again during puberty, declining slowly through adult life[16,39]. **b**, Healthy centenarians have fourfold higher serum levels of ALS than unhealthy control individuals (drawn using data from ref. 47). **c**, Hepatic *IGFALS* expression is 50% lower in older (>74 years, median age 79 years) than in younger (<49 years, median age 34 years) humans (drawn using data from ref. 50). **d**, The increased adipose tissue mass and decreased lean mass, seen in ageing normal wild-type (WT) mice, are absent in *Igfals* knockout (KO) mice[85]. **e**, Across 21 strains of dwarf mice, hepatic *Igfals* expression is inversely correlated with lifespan, a trend not seen for *Igf1* (ref. 86). Refer to cited articles for further details and unmodified versions of these data. Part **d** adapted from ref. 85, Springer Nature Limited. Part **e** adapted from ref. 86, CC BY 4.0.

by 4 weeks of IGF-1 administration, providing new support for the importance of endocrine IGF-1 in bone development[82]. Parathyroid hormone administration revealed differences between bone compartments among control, LID, ALSKO and ALSKO–LID strains. For example, cortical bone area was increased by parathyroid hormone in control and *Igfals*-null mice but not in the LID or ALSKO–LID strains, whereas parathyroid hormone had no effect on the trabecular bone volume to total volume fraction in either *Igfals*-null strain. This finding suggested that the circulating form of IGF-1 (determined by ALS) rather than just its concentration was important in bone growth and the bone response to parathyroid hormone[83]. In addition to its endocrine role in regulating bone metabolism, ALS might have a direct action at the level of osteogenesis by regulating the differentiation of bone-marrow-derived mesenchymal stem cells. Mesenchymal stem cells from ALSKO mice showed increased adipogenic differentiation compared with mesenchymal stem cells from control mice, accompanied by increased PPARγ expression; furthermore, exogenous recombinant ALS suppressed adipogenesis. Conversely, osteogenic differentiation was markedly decreased in ALSKO-derived mesenchymal stem cells (Table 1), which suggests a direct role for ALS in controlling mesenchymal stem cell fate[84].

A comparison of ageing ALSKO and wild-type mice between 1 and 2 years old showed significantly lower body weight in the absence of *Igfals*, with lower adipose tissue mass and higher lean mass[85] (Fig. 3d). In the femurs of 2-year-old ALSKO mice, the marked intracortical porosity that is characteristic of 2-year-old wild-type mice was absent, corresponding to fewer osteoclasts in the absence of *Igfals*, with bone stiffness and strength significantly increased[85]. It is possible that these differences are attributable to the lifelong reduced IGF-1 levels in the circulation, although hepatic *Igf1* expression is unaffected by *Igfals* deletion[81]. An increased incidence of hepatic and gastric tumours was also observed in 2-year-old ALSKO mice compared with control mice, perhaps related to increased GH secretion[85]. However, it is notable that *Igfals* has been identified as a longevity-associated gene in GH-deficient dwarf mutant mouse strains (such as Ames and Snell) and shows a significant negative correlation with mean lifespan across 21 dwarf strains; this association is not seen for *Igf1* (ref. 86) (Fig. 3e). Whether this finding represents an independent effect of *Igfals* or simply reflects the central role of ALS in IGF transport remains to be established. Contrasting with these findings, in a mouse model of premature ageing resulting from deletion of *Zmpste24* (encoding a metalloproteinase), *Igfals* expression was strongly downregulated[87].

In other ALS-null animal models, zebrafish lacking *Igfals* during development showed increased dorsalization (for example, truncation of the tail and other morphological changes) that could be rescued by human ALS mRNA, which indicates a role for ALS in dorsoventral patterning[34]. In *Drosophila*, dALS silencing had no effect on larval development but reduced adult male size[80]. Furthermore, in two *Drosophila* models of Alzheimer neurodegeneration, dALS knockdown exacerbated the degree of neuronal dysfunction[88] (Table 1). These findings are suggestive of cellular ALS actions beyond the regulation of IGF transport. Such actions could be at the level of the extracellular matrix as human ALS has been identified as a matrisomal protein[64] and dALS is involved in matrix organization[22].

IGFALS mutation in humans

Apart from defects in GH synthesis or signalling, *IGFALS* mutations have emerged as a notable cause of IGF-1 deficiency. The first report described a frameshift mutation encoding a severely truncated protein, which was undetectable in the serum of the protein either immunologically or by the presence of an IGF ternary complex. As seen in *Igfals*-null mice, despite extremely low circulating levels of IGF-1 and IGFBP-3, growth impairment was not severe (about −2 SD); however, some pubertal delay was present[89] (Table 1). This report was followed by the description of a patient with similar growth characteristics and similarly low levels of IGF-1 and IGFBP-3, which was attributed to a missense mutation resulting in undetectable serum levels of ALS[90]. In vitro, this mutation (Asp440Asn, numbered including the signal peptide) was shown to generate a new glycosylation site on ALS, with impaired secretion and deficient ternary complex formation[91]. Engineering a second mutation to block glycosylation at Asn440 only slightly alleviated the secretion defect but fully restored the ability to form a ternary complex with IGF-1 and IGFBP-3 in vitro. This finding provided the first mechanistic demonstration of how a natural ALS mutation could disrupt IGF transport.

Since these two reports were published, there have been many descriptions of *IGFALS* mutations, as extensively discussed

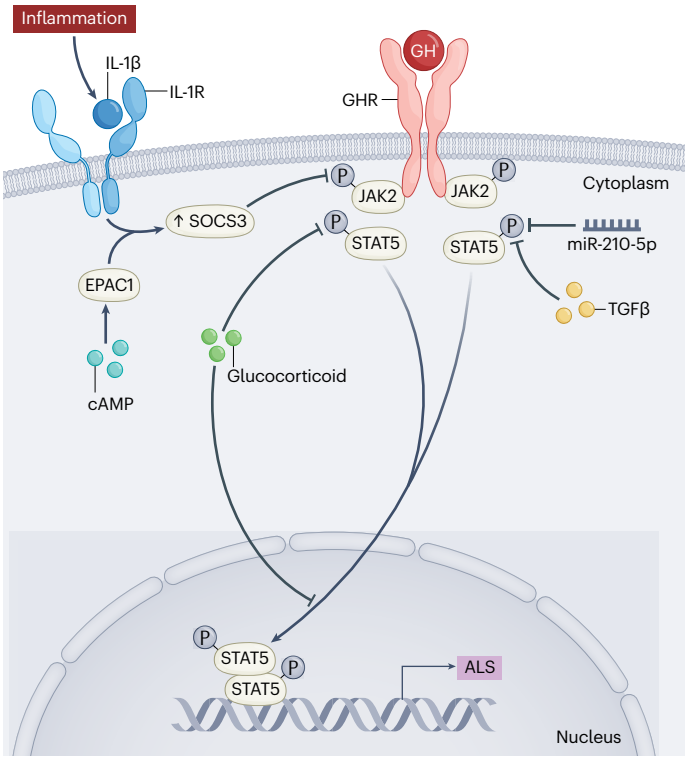

Fig. 4 | Regulation of acid-labile subunit synthesis. Growth hormone (GH) signals through the GH receptor (GHR), mediated by JAK2 and STAT5 activation, to stimulate transcription of *IGFALS*, the gene encoding acid-labile subunit (ALS)[57,58]. The inflammatory cytokine IL-1β[143] induces expression of *SOCS3*, which inhibits JAK2 signalling[163], thereby blocking *IGFALS* transcription. Similarly, cAMP, which leads to induction of *SOCS3* expression through the exchange protein activated by cAMP 1 (EPAC1)[164], inhibits *IGFALS* expression and protein levels of ALS[61]. Inhibition of STAT5-mediated transcription by transforming growth factor-β (TGFβ)[165] and glucocorticoids[166] might account for their inhibitory effects on ALS synthesis in hepatocytes[55,59]. The microRNA miR-210-5p might contribute to the suppression of ALS in hepatocellular carcinoma[120] by targeting STAT5 (ref. 167).

Table 1 | Acid-labile subunit deletion phenotypes

Species	Phenotype	Refs.
Drosophila	No effect on larval development; reduced adult male size	80
	Exacerbated neuronal dysfunction in Alzheimer disease models	88
Zebrafish	Increased dorsalization (for example, shortened trunk and loss of tail)	34
Mouse	Mild effect on postnatal growth; decreased serum levels of IGF-1 and IGFBP-3[a]	81
	Increased IGF-1 clearance; decreased femoral length, density, cross-sectional area, cortical thickness and so on	82
	Increased vertebral trabecular number and bone volume fraction	83
	Decreased osteogenesis, increased adipogenesis by mesenchymal stromal cells	84
	During ageing, lower adipose tissue mass and higher lean mass than control mice	85
	No insulin resistance; improved glucose clearance compared with control mice	103
Human[b]	Growth retardation, delayed puberty, insulin resistance, low levels of IGF-1 and IGFBP-3	89,95
	Low head circumference, low bone mineral density	94,95

IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein. [a]The *Igfals* inactivation model described in this study is the basis of all *Igfals*-null mouse models described in this table. [b]These studies refer to various *IGFALS* mutations but all result in a loss of acid-labile subunit protein.

elsewhere[92–100]. Up to 2023, the Human Gene Mutation Database reported 35 mutations, of which the majority are missense or nonsense (Fig. 1). The elucidation of the IGF–IGFBP-3–ALS ternary complex structure has provided structural explanations for the probable deleterious effects of many of these mutations on ALS function[21]. In general, the typical growth phenotype of affected individuals is quite similar and shows a gene dosage effect: about −2 SD in height for mutation in both alleles (range: −0.5 to −4.2) and about −1 SD for a heterozygous mutation (range: +1.6 to −3.3)[93]. This gene dosage effect is also evident in the extent of reduction in serum levels of IGF-1, IGFBP-3 and ALS in those with homozygous mutations compared with those with heterozygous mutations[101]. Treatment of patients with a biallelic *IGFALS* mutation with recombinant human GH has shown disappointing results with, at best, small effects on growth[100]. A satisfactory growth response to human GH administration has been reported in a patient with short stature who had a heterozygous *IGFALS* mutation; as such, further investigation of the efficacy of this treatment in people with heterozygous *IGFALS* mutations is warranted[102].

In addition to growth impairment, *IGFALS* mutations are sometimes associated with low head circumference[94,97], low bone mineral density[92,94], insulin insensitivity and delayed puberty[92,95] (Table 1). A statistically significant gene dosage effect has been reported for some bone parameters, but not for parameters of carbohydrate or lipid metabolism[101]. The mild insulin resistance in the absence of ALS contrasts with the finding in ALSKO mice, which have no hyperinsulinaemia and have faster glucose clearance than control mice[103]. In addition to low circulating levels of IGFBP-3 in humans with ALS deficiency, IGFBP-1 and IGFBP-2 are typically also low[92]; however, the reason is unclear as neither is known to interact with ALS.

ALS in human disease

GH disorders

As circulating levels of ALS are low in GHD and increased in conditions of GH excess, ALS has been evaluated extensively in disorders that affect GH. When used to monitor the effectiveness of increasing human GH dose levels to normalize serum markers in adults with GHD, ALS measurement performed similarly to IGFBP-3 measurement, but not as sensitively as IGF-1 measurement[104]. Although IGF-1 and ALS levels remained associated over 12 months of treatment (while the relationship between IGF-1 and IGFBP-3 levels was lost)[105], it has been concluded that neither IGFBP-3 nor ALS measurement offers any benefit over monitoring IGF-1 alone[106]. ALS is also not regarded as particularly effective in diagnosing adult GHD, as there is considerable overlap between healthy and GHD values[107,108]. ALS measurement can be used to monitor GH replacement in children with GHD[76], but is regarded as less useful than IGF-1 or IGFBP-3 in diagnosing paediatric GHD[109,110]. An expert opinion, published in 2023, on the diagnosis of GHD in adults or children does not include measurement of ALS[111].

In diagnosing patients with GH excess owing to acromegaly, ALS measurement, with an area under the receiver operating characteristic curve of 0.937, was less sensitive than measuring IGF-1, although better than measuring IGFBP-3 (the normal range for IGFBP-3 overlaps with that seen in acromegaly)[112]. After surgery, all patients whose surgery was considered successful showed ALS values in the normal range[112], suggesting its value as a marker of disease activity[113]. However, another study found that testing for ALS offered no benefit over measuring IGF-1 (ref. 108). ALS measurement is not included in current consensus recommendations for the management of patients with acromegaly[114]. ALS has also been evaluated for its ability to detect exogenous GH administration in athletes. Although levels of ALS increase in response to GH in a similar way to IGF-1 levels[115], approved GH doping protocols do not currently include ALS measurement[116].

Cancer

Hepatocellular carcinoma. *IGFALS* has been proposed as a potential tumour suppressor gene in patients with hepatocellular carcinoma on the basis of its CpG hypermethylation, which has been associated with a loss of genomic information[117,118]. *IGFALS* seems to be progressively downregulated as hepatocellular carcinoma develops from healthy liver, progressing through low-grade and high-grade dysplastic nodules to early and then advanced hepatocellular carcinoma[119]. In hepatocellular carcinoma positive for hepatitis B virus, low ALS levels have been attributed to its potential suppression by the microRNA miR-210-5p, which is upregulated in these carcinomas[120] (Fig. 4). Several studies report that *IGFALS* has prognostic potential in hepatocellular carcinoma, with low levels of *IGFALS* expression predicting poor patient survival[121,122]. Conversely, high expression of *IGFALS* is reported to be a marker for small tumour size, low tumour, node and metastasis staging and extended overall or progression-free survival[35]. In alcoholic liver disease, a common precursor of hepatocellular carcinoma, ALS is strongly downregulated and is a powerful predictor of severe versus non-severe disease, with a specificity of 1.00 and a sensitivity of 0.92 (ref. 123).

Prostate and breast cancer. The relative risk of advanced prostate cancer could be higher for men in the middle or high tertiles for plasma levels of ALS than for men with the lowest ALS levels. However, this risk is modified by IGF-1 levels; for example, men with IGF-1 levels in the

highest tertile and low ALS levels have a higher relative risk of advanced prostate cancer (relative risk of 9.3) than those with the highest ALS and IGF-1 levels (relative risk of 5.0)[124]. By contrast, another study found no statistically significant association between ALS levels and lethal prostate cancer risk[125]. An *IGFALS* polymorphism (rs17559) showed a significant association with survival related to prostate cancer, with hazard ratios reported as 0.72 for people heterozygous for the polymorphism and 0.41 for those with minor homozygous polymorphisms[126]; however, a subsequent study did not find any ALS polymorphisms that were associated with mortality related to prostate cancer[127].

In The Cancer Genome Atlas breast cancer data, *IGFALS* expression is statistically significantly elevated in breast cancer tissue compared with normal breast tissue, in parallel with hypomethylation in the *IGFALS* promoter region[128]. However, high *IGFALS* expression predicts improved overall survival in patients with invasive breast cancer[129]. In addition, *IGFALS* has been included in predictive gene panels that have high accuracy in determining patient prognosis[129,130]. No *IGFALS* polymorphisms have been shown to associate with breast cancer risk, patient survival or mammographic density[131–133].

Non-islet cell tumour hypoglycaemia. Hypoglycaemia associated with extrapancreatic tumours, or non-islet cell tumour hypoglycaemia, was recognized as a disorder involving IGFs five decades ago. Non-islet cell tumour hypoglycaemia is attributed to the tumour producing incompletely processed IGF-2 precursors, sometimes termed 'big' IGF-2 (refs. 134–136). Serum levels of ALS are less than half of normal in patients with non-islet cell tumour hypoglycaemia, and IGFBP-3 circulates largely in binary, rather than the usual ternary, complexes in these patients[137]. In vitro, the addition of ALS to serum from patients with non-islet cell tumour hypoglycaemia largely restores the ternary complexes[138]. Moreover, treatment of patients with GH to restore ALS levels (as first proposed by Teale et al.[139]) alleviates the hypoglycaemia[140,141], which suggests that there is a functional deficiency of ALS in these patients. Although patient-derived big IGF-2 forms normal binary complexes with IGFBP-3 and IGFBP-5, the binary complexes that include IGFBP-3 bind ALS extremely poorly, whereas those that include IGFBP-5 seem to bind normally[142]. Poor ternary complex formation by IGFBP-3 in non-islet cell tumour hypoglycaemia might increase the bioavailability of IGF-2, contributing to hypoglycaemia in this condition.

Inflammation, sepsis and COVID

In rat hepatocyte cultures stimulated with GH, the pro-inflammatory cytokine IL-1β markedly suppresses synthesis and secretion of ALS, mediated by the induction of suppressor of cytokine signalling 3 (SOCS3)[62,63,143] (Fig. 4). In vivo, rats treated with endotoxin initially show suppressed ALS levels, after a spike in SOCS3 and suppression of GH receptor mRNA at 12 h, eventually followed by a rebound in ALS above initial levels[63,144]. Similarly, patients admitted to an intensive care unit show an initial drop in serum levels of ALS, which only recover above baseline in the subset of patients in whom IGF-1 levels also rebound[145]. During protracted critical illness, ALS levels fall lower in men than in women, an effect attributed to lower GH pulsatility in men than in women for the same total GH production[146]. ALS levels are strongly associated with the pulsatile, but not the non-pulsatile, GH fraction[146].

ALS has been evaluated preclinically as a biomarker for inflammatory cytokine expression[147]. In addition, in patients with sepsis, ALS is statistically significantly associated with mortality attributed to septic shock and is included in a highly specific proteomic panel associated with mortality[148]. Similarly, serum levels of ALS decline in patients with severe rheumatic heart disease, and the inclusion of ALS in a 6-protein panel allows the correct classification of more than 90% of patients[149].

In cell culture studies, viral infection increases ALS levels in cell lysates, which is proposed to contribute to the antiviral immune response[150]. However, in patients with COVID-19, serum levels of ALS decline as infection progresses from non-severe to severe and decline across uninfected individuals, those who survive COVID-19 and those who do not survive; therefore, ALS might be predictive of disease progression and patient survival[151,152]. ALS might act as a prognostic marker in COVID-19 (low levels are associated with poor prognosis), reflecting levels of inflammatory cytokines[153], and it is included in a proteomic panel predicting mortality in patients with COVID-19[154] (Box 1). An apparently contrasting study found that ALS levels were statistically significantly increased in patients with COVID-19 who progressed to critical illness, compared with the non-critical group[155].

Cardiovascular and metabolic disorders

Serum levels of ALS were initially reported to be elevated in men with coronary heart disease (but not diabetes mellitus), along with IGFBP-3 and IGFBP-5 (ref. 156). However, a subsequent plasma proteome study from the Women's Health Initiative showed decreased levels of ALS in those with coronary heart disease compared with control individuals[157]. Hypertrophic cardiomyopathy sometimes progresses to heart failure, and ALS was found to be statistically significantly decreased in patients with acute heart failure with preserved ejection fraction compared with those who had hypertrophic cardiomyopathy[158]. Interestingly, in a plasma proteomic analysis, a hazard ratio of 0.65 was seen for the association between ALS and heart failure after myocardial infarction[159] (that is, ALS levels are inversely associated with the risk of heart failure). As there are no mechanistic studies relating ALS to cardiovascular disease, it is unclear whether the link is through altered IGF dynamics or an unrelated cellular mechanism. Patients with non-valvular atrial

Box 1

Proteomic studies of serum acid-labile subunit abundance in patients with COVID-19

- The acid labile subunit (ALS) is downregulated in severe disease; ALS levels are potentially prognostic for disease progression[151].
- Levels of ALS are higher in those who survive a COVID-19 infection than in those who do not; ALS is part of a protein panel for mortality risk assessment[152,154].
- Low levels of ALS are associated with severe COVID-19. ALS is prognostic for severe COVID-19; this association has been confirmed by enzyme-linked immunosorbent assay[153].
- ALS concentrations are higher in patients who have pneumonia associated with COVID-19 and are critically ill than in those who are not critically ill[155].
- ALS concentrations are higher in control individuals who test negative for COVID-19 than in patients who test positive[168].

fibrillation have about 20-fold lower ALS mRNA expression in platelets than control individuals, rebounding over 250-fold after treatment (pulmonary vein isolation)[160]. In this instance, it was proposed that platelet-derived ALS acts by modulating the IGF environment, possibly locally, as IGF-1 is known to stimulate platelet aggregation; however, this hypothesis has not been tested experimentally.

The association between ALS deficiency and insulin insensitivity in humans has already been mentioned in the section '*IGFALS* mutation in humans'[92]. In brief, although fasting blood levels of glucose are sometimes normal in people with ALS deficiency, hyperinsulinaemia and glucose intolerance are often observed. These findings contrast with those in ALSKO mice, which show improved glucose tolerance compared with control mice[103]. In patients with insulin-dependent diabetes mellitus, serum levels of ALS are decreased, and they are restored by insulin therapy[161]; similar findings are seen in rats with streptozotocin-induced diabetes mellitus[48]. In a study of patients with type 2 diabetes mellitus, serum levels of ALS were negatively associated with levels of LDL cholesterol and insulin sensitivity and were positively associated with fasting levels of insulin. In this study, treatment with rosiglitazone for 24 weeks caused a marked reduction in ALS in patients without obesity, but not in those who had obesity. Changes in ALS levels on treatment were reported to predict changes in total cholesterol levels[162]. The inverse association between ALS levels and insulin sensitivity in type 2 diabetes mellitus seems contrary to the apparent insulin resistance seen in people with mutations in *IGFALS* who have no circulating ALS, which suggests that a lifelong disruption of the IGF axis in ALS deficiency might cause additional metabolic impairment.

Conclusions

For about two decades after its existence was first proposed in 1980 (ref. 5), ALS research was largely confined to biochemical investigations of its ternary complexes, cell biology and preclinical studies of its regulation, as well as immunoassays of serum levels in various clinical conditions. Although these studies established a firm foundation for understanding the endocrine biology of ALS, they did not uncover the deeper insights that have begun to emerge in the past few years. For example, the structural determination by cryo-EM[21] has provided critical new information on ALS and the ternary complex structure and could provide a more nuanced understanding of IGF, IGFBP-3 and ALS physiology and pathology than was previously possible. In vivo studies involving deletion or inactivation of the gene that encodes ALS, whether by natural mutation in humans or experimentally in mice, zebrafish or *Drosophila*, have revealed a wealth of new knowledge on the wide-ranging actions of ALS not only in somatic growth but also in development, bone and carbohydrate metabolism and some cancers. Finally, a plethora of proteomic studies have, often inadvertently, uncovered an unexpected involvement of ALS in diverse conditions, including COVID-19 and cardiovascular disease.

Despite these advances, many important research questions remain. For example, to date, there is no detailed structural information about ALS complexes with IGFBP-5, or about complexes with proteolysed IGFBP-3 (as is seen in the serum of pregnant people). At the cell biology level, possible roles of ALS as a matrisomal protein are almost entirely unknown. Finally, both preclinically and clinically, emerging relationships between ALS and both longevity and cancer require further exploration, and differences between mouse and human studies on the effects of ALS deletion in metabolic disease need to be better understood. The exciting discoveries described in this Review suggest that the focus to date on ALS as a key player in the endocrinology of growth might have underestimated the diversity of its actions and indicate that we are on the threshold of a much broader understanding of its importance in human and animal biology and pathology.

Published online: 21 March 2024

References

1. Bürgi, H., Müller, W. A., Humbel, R. E., Labhart, A. & Froesch, E. R. Non-suppressible insulin-like activity of human serum. I. Physicochemical properties, extraction and partial purification. *Biochim. Biophys. Acta* **121**, 349–359 (1966).
2. Zapf, J., Waldvogel, M. & Froesch, E. R. Binding of nonsuppressible insulin-like activity to human serum. Evidence for a carrier protein. *Arch. Biochem. Biophys.* **168**, 638–645 (1975).
3. Hintz, R. L. & Liu, F. Demonstration of specific plasma protein binding sites for somatomedin. *J. Clin. Endocrinol. Metab.* **45**, 988–995 (1977).
4. Wilkins, J. R. & D'Ercole, A. J. Affinity-labeled plasma somatomedin-C/insulin-like growth factor I binding proteins. Evidence of growth hormone dependence and subunit structure. *J. Clin. Invest.* **75**, 1350–1358 (1985).
5. Furlanetto, R. W. The somatomedin C binding protein: evidence for a heterologous subunit structure. *J. Clin. Endocrinol. Metab.* **51**, 12–19 (1980).
6. Hintz, R. L. Plasma forms of somatomedin and the binding protein phenomenon. *Clin. Endocrinol. Metab.* **13**, 31–42 (1984).
7. Martin, J. L. & Baxter, R. C. Insulin-like growth factor-binding protein from human plasma. Purification and characterization. *J. Biol. Chem.* **261**, 8754–8760 (1986).
8. Wood, W. I. et al. Cloning and expression of the growth hormone-dependent insulin-like growth factor-binding protein. *Mol. Endocrinol.* **2**, 1176–1185 (1988).
9. Baxter, R. C. Characterization of the acid-labile subunit of the growth hormone-dependent insulin-like growth factor binding protein complex. *J. Clin. Endocrinol. Metab.* **67**, 265–272 (1988).
10. Baxter, R. C., Martin, J. L. & Beniac, V. A. High molecular weight insulin-like growth factor binding protein complex. Purification and properties of the acid-labile subunit from human serum. *J. Biol. Chem.* **264**, 11843–11848 (1989).
11. Leong, S. R., Baxter, R. C., Camerato, T., Dai, J. & Wood, W. I. Structure and functional expression of the acid-labile subunit of the insulin-like growth factor-binding protein complex. *Mol. Endocrinol.* **6**, 870–876 (1992).
12. Baxter, R. C. & Martin, J. L. Structure of the Mr 140,000 growth hormone-dependent insulin-like growth factor binding protein complex: determination by reconstitution and affinity-labeling. *Proc. Natl Acad. Sci. USA* **86**, 6898–6902 (1989).
13. Cohen, K. L. & Nissley, S. P. The serum half-life of somatomedin activity: evidence for growth hormone dependence. *Acta Endocrinol.* **83**, 243–258 (1976).
14. Franklin, R. C., Rennie, G. C., Burger, H. G. & Cameron, D. P. Changes in NSILA-S in response to somatotropin administration and hypophysectomy. *J. Clin. Endocrinol. Metab.* **47**, 91–96 (1978).
15. Baxter, R. C. & Martin, J. L. Radioimmunoassay of growth hormone-dependent insulin-like growth factor binding protein in human plasma. *J. Clin. Invest.* **78**, 1504–1512 (1986).
16. Baxter, R. C. Circulating levels and molecular distribution of the acid-labile (alpha) subunit of the high molecular weight insulin-like growth factor-binding protein complex. *J. Clin. Endocrinol. Metab.* **70**, 1347–1353 (1990).
17. Bella, J., Hindle, K. L., McEwan, P. A. & Lovell, S. C. The leucine-rich repeat structure. *Cell Mol. Life Sci.* **65**, 2307–2333 (2008).
18. Matsushima, N., Takatsuka, S., Miyashita, H. & Kretsinger, R. H. Leucine rich repeat proteins: sequences, mutations, structures and diseases. *Protein Pept. Lett.* **26**, 108–131 (2019).
19. Janosi, J. B. et al. The acid-labile subunit of the serum insulin-like growth factor-binding protein complexes. Structural determination by molecular modeling and electron microscopy. *J. Biol. Chem.* **274**, 23328–23332 (1999).
20. David, A., Kelley, L. A. & Sternberg, M. J. A new structural model of the acid-labile subunit: pathogenetic mechanisms of short stature-causing mutations. *J. Mol. Endocrinol.* **49**, 213–220 (2012).
21. Kim, H. et al. Structural basis for assembly and disassembly of the IGF/IGFBP/ALS ternary complex. *Nat. Commun.* **13**, 4434 (2022).
22. Swanson, L. E. et al. *Drosophila* convoluted/dALS is an essential gene required for tracheal tube morphogenesis and apical matrix organization. *Genetics* **181**, 1281–1290 (2009).
23. Rotwein, P. Large-scale analysis of variation in the insulin-like growth factor family in humans reveals rare disease links and common polymorphisms. *J. Biol. Chem.* **292**, 9252–9261 (2017).
24. Janosi, J. B., Firth, S. M., Bond, J. J., Baxter, R. C. & Delhanty, P. J. N-linked glycosylation and sialylation of the acid-labile subunit. Role in complex formation with insulin-like growth factor (IGF)-binding protein-3 and the IGFs. *J. Biol. Chem.* **274**, 5292–5298 (1999).
25. Holman, S. R. & Baxter, R. C. Insulin-like growth factor binding protein-3: factors affecting binary and ternary complex formation. *Growth Regul.* **6**, 42–47 (1996).
26. Lee, C. Y. & Rechler, M. M. Purified rat acid-labile subunit and recombinant human insulin-like growth factor (IGF)-binding protein-3 can form a 150-kilodalton binary complex in vitro in the absence of IGFs. *Endocrinology* **136**, 4982–4989 (1995).

27. Choi, K. Y. & Lee, D. H. Interaction between acid-labile subunit and insulin-like growth factor binding protein 3 expressed in *Xenopus* oocytes. *J. Biochem. Mol. Biol.* **35**, 186–193 (2002).
28. Firth, S. M., Ganeshprasad, U. & Baxter, R. C. Structural determinants of ligand and cell surface binding of insulin-like growth factor-binding protein-3. *J. Biol. Chem.* **273**, 2631–2638 (1998).
29. Twigg, S. M. & Baxter, R. C. Insulin-like growth factor (IGF)-binding protein 5 forms an alternative ternary complex with IGFs and the acid-labile subunit. *J. Biol. Chem.* **273**, 6074–6079 (1998).
30. Twigg, S. M., Kiefer, M. C., Zapf, J. & Baxter, R. C. Insulin-like growth factor-binding protein 5 complexes with the acid-labile subunit. Role of the carboxyl-terminal domain. *J. Biol. Chem.* **273**, 28791–28798 (1998).
31. Chin, E., Zhou, J., Dai, J., Baxter, R. C. & Bondy, C. A. Cellular localization and regulation of gene expression for components of the insulin-like growth factor ternary binding protein complex. *Endocrinology* **134**, 2498–2504 (1994).
32. Kim, J. W. et al. Isolation of the cDNA encoding the acid labile subunit (ALS) of the 150 kDa IGF-binding protein complex in cattle and ALS regulation during the transition from pregnancy to lactation. *J. Endocrinol.* **189**, 583–593 (2006).
33. Lee, C. Y. et al. Molecular cloning of the porcine acid-labile subunit (ALS) of the insulin-like growth factor-binding protein complex and detection of ALS gene expression in hepatic and non-hepatic tissues. *J. Mol. Endocrinol.* **26**, 135–144 (2001).
34. Landi, E. et al. Expression of acid-labile subunit (ALS) in developing and adult zebrafish and its role in dorso-ventral patterning during development. *Gen. Comp. Endocrinol.* **299**, 113591 (2020).
35. Chen, W. et al. The matrisome genes from hepatitis B-related hepatocellular carcinoma unveiled. *Hepatol. Commun.* **5**, 1571–1585 (2021).
36. Naba, A. et al. The extracellular matrix: tools and insights for the 'omics' era. *Matrix Biol.* **49**, 10–24 (2016).
37. Ouni, E., Vertommen, D., Chiti, M. C., Dolmans, M. M. & Amorim, C. A. A draft map of the human ovarian proteome for tissue engineering and clinical applications. *Mol. Cell Proteom.* **18**, S159–S173 (2019).
38. Wilczak, N. et al. Insulin-like growth factor (IGF)-I binding to a cell membrane associated IGF binding protein-3 acid-labile subunit complex in human anterior pituitary gland. *J. Neurochem.* **82**, 430–438 (2002).
39. Lewitt, M. S. et al. Regulation of insulin-like growth factor-binding protein-3 ternary complex formation in pregnancy. *J. Endocrinol.* **159**, 265–274 (1998).
40. Lo, H. C. et al. Relation of cord serum levels of growth hormone, insulin-like growth factors, insulin-like growth factor binding proteins, leptin, and interleukin-6 with birth weight, birth length, and head circumference in term and preterm neonates. *Nutrition* **18**, 604–608 (2002).
41. Juul, A. et al. The acid-labile subunit of human ternary insulin-like growth factor binding protein complex in serum: hepatosplanchnic release, diurnal variation, circulating concentrations in healthy subjects, and diagnostic use in patients with growth hormone deficiency. *J. Clin. Endocrinol. Metab.* **83**, 4408–4415 (1998).
42. Stadler, S. et al. Monoclonal anti-acid-labile subunit oligopeptide antibodies and their use in a two-site immunoassay for ALS measurement in humans. *J. Immunol. Methods* **252**, 73–82 (2001).
43. Frystyk, J. et al. Developmental changes in serum levels of free and total insulin-like growth factor I (IGF-I), IGF-binding protein-1 and -3, and the acid-labile subunit in rats. *Endocrinology* **139**, 4286–4292 (1998).
44. Baxter, R. C. & Dai, J. Purification and characterization of the acid-labile subunit of rat serum insulin-like growth factor binding protein complex. *Endocrinology* **134**, 848–852 (1994).
45. Hwang, D. L., Lee, P. D. & Cohen, P. Quantitative ontogeny of murine insulin-like growth factor (IGF)-I, IGF-binding protein-3 and the IGF-related acid-labile subunit. *Growth Horm. IGF Res.* **18**, 65–74 (2008).
46. Baxter, R. C. Signaling pathways of the insulin-like growth factor binding proteins. *Endocr. Rev.* **44**, 753–778 (2023).
47. Santos-Lozano, A. et al. Successful aging: insights from proteome analyses of healthy centenarians. *Aging* **12**, 3502–3515 (2020).
48. Dai, J. & Baxter, R. C. Regulation in vivo of the acid-labile subunit of the rat serum insulin-like growth factor-binding protein complex. *Endocrinology* **135**, 2335–2341 (1994).
49. Lee, C. Y., Cohen, F. J., Wu, H. B., Ooi, G. T. & Rechler, M. M. The absence of 150-kDa insulin-like growth factor complexes in fetal rat serum is not due to a lack of functional acid-labile subunit. *Horm. Metab. Res.* **31**, 182–185 (1999).
50. Schreiter, T. et al. Transcriptome-wide analysis of human liver reveals age-related differences in the expression of select functional gene clusters and evidence for a PPP1R10-governed 'aging cascade'. *Pharmaceutics* **13**, 2009 (2021).
51. Mandel, S. H., Moreland, E., Rosenfeld, R. G. & Gargosky, S. E. The effect of GH therapy on the immunoreactive forms and distribution of IGFBP-3, IGF-I, the acid-labile subunit, and growth rate in GH-deficient children. *Endocrine* **7**, 351–360 (1997).
52. Gargosky, S. E., Tapanainen, P. & Rosenfeld, R. G. Administration of growth hormone (GH), but not insulin-like growth factor-I (IGF-I), by continuous infusion can induce the formation of the 150-kilodalton IGF-binding protein-3 complex in GH-deficient rats. *Endocrinology* **134**, 2267–2276 (1994).
53. Scharf, J., Ramadori, G., Braulke, T. & Hartmann, H. Synthesis of insulin-like growth factor binding proteins and of the acid-labile subunit in primary cultures of rat hepatocytes, of Kupffer cells, and in cocultures: regulation by insulin, insulinlike growth factor, and growth hormone. *Hepatology* **23**, 818–827 (1996).
54. Olivecrona, H. et al. Acute and short-term effects of growth hormone on insulin-like growth factors and their binding proteins: serum levels and hepatic messenger ribonucleic acid responses in humans. *J. Clin. Endocrinol. Metab.* **84**, 553–560 (1999).
55. Dai, J., Scott, C. D. & Baxter, R. C. Regulation of the acid-labile subunit of the insulin-like growth factor complex in cultured rat hepatocytes. *Endocrinology* **135**, 1066–1072 (1994).
56. Ooi, G. T., Cohen, F. J., Tseng, L. Y., Rechler, M. M. & Boisclair, Y. R. Growth hormone stimulates transcription of the gene encoding the acid-labile subunit (ALS) of the circulating insulin-like growth factor-binding protein complex and ALS promoter activity in rat liver. *Mol. Endocrinol.* **11**, 997–1007 (1997).
57. Ooi, G. T., Hurst, K. R., Poy, M. N., Rechler, M. M. & Boisclair, Y. R. Binding of STAT5a and STAT5b to a single element resembling a gamma-interferon-activated sequence mediates the growth hormone induction of the mouse acid-labile subunit promoter in liver cells. *Mol. Endocrinol.* **12**, 675–687 (1998).
58. Sos, B. C. et al. Abrogation of growth hormone secretion rescues fatty liver in mice with hepatocyte-specific deletion of JAK2. *J. Clin. Invest.* **121**, 1412–1423 (2011).
59. Barreca, A. et al. Functions and regulation of the acid-labile subunit of the 150 K complex. *Prog. Growth Factor. Res.* **6**, 231–239 (1995).
60. Scharf, J. G., Braulke, T., Hartmann, H. & Ramadori, G. Regulation of the components of the 150 kDa IGF binding protein complex in cocultures of rat hepatocytes and Kupffer cells by 3′,5′-cyclic adenosine monophosphate. *J. Cell Physiol.* **186**, 425–436 (2001).
61. Delhanty, P. J. & Baxter, R. C. The regulation of acid-labile subunit gene expression and secretion by cyclic adenosine 3′,5′-monophosphate. *Endocrinology* **139**, 260–265 (1998).
62. Delhanty, P. J. Interleukin-1 beta suppresses growth hormone-induced acid-labile subunit mRNA levels and secretion in primary hepatocytes. *Biochem. Biophys. Res. Commun.* **243**, 269–272 (1998).
63. Barreca, A., Ketelslegers, J. M., Arvigo, M., Minuto, F. & Thissen, J. P. Decreased acid-labile subunit (ALS) levels by endotoxin in vivo and by interleukin-1beta in vitro. *Growth Horm. IGF Res.* **8**, 217–223 (1998).
64. Hynes, R. O. & Naba, A. Overview of the matrisome — an inventory of extracellular matrix constituents and functions. *Cold Spring Harb. Perspect. Biol.* **4**, a004903 (2012).
65. Fernqvist-Forbes, E., Ekberg, K., Lindgren, B. F. & Brismar, K. Splanchnic exchange of insulin-like growth factor binding protein-1 (IGFBP-1), IGF-I and acid-labile subunit (ALS) during normo- and hyper-insulinaemia in healthy subjects. *Clin. Endocrinol.* **51**, 327–332 (1999).
66. Juul, A. et al. Serum levels of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in healthy infants, children, and adolescents: the relation to IGF-I, IGF-II, IGFBP-1, IGFBP-2, age, sex, body mass index, and pubertal maturation. *J. Clin. Endocrinol. Metab.* **80**, 2534–2542 (1995).
67. Van den Berghe, G. et al. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. *J. Clin. Endocrinol. Metab.* **84**, 1311–1323 (1999).
68. Lewitt, M. S., Saunders, H., Phuyal, J. L. & Baxter, R. C. Complex formation by human insulin-like growth factor-binding protein-3 and human acid-labile subunit in growth hormone-deficient rats. *Endocrinology* **134**, 2404–2409 (1994).
69. Lewitt, M. S., Saunders, H. & Baxter, R. C. Bioavailability of insulin-like growth factors (IGFs) in rats determined by the molecular distribution of human IGF-binding protein-3. *Endocrinology* **133**, 1797–1802 (1993).
70. Zapf, J., Hauri, C., Waldvogel, M. & Froesch, E. R. Acute metabolic effects and half-lives of intravenously administered insulin-like growth factors I and II in normal and hypophysectomized rats. *J. Clin. Invest.* **77**, 1768–1775 (1986).
71. Firth, S. M., McDougall, F., McLachlan, A. J. & Baxter, R. C. Impaired blockade of insulin-like growth factor I (IGF-I)-induced hypoglycemia by IGF binding protein-3 analog with reduced ternary complex-forming ability. *Endocrinology* **143**, 1669–1676 (2002).
72. Payet, L. D., Firth, S. M. & Baxter, R. C. The role of the acid-labile subunit in regulating insulin-like growth factor transport across human umbilical vein endothelial cell monolayers. *J. Clin. Endocrinol. Metab.* **89**, 2382–2389 (2004).
73. Xu, S. et al. Insulin-like growth factors (IGFs) and IGF-binding proteins in human skin interstitial fluid. *J. Clin. Endocrinol. Metab.* **80**, 2940–2945 (1995).
74. Hughes, S. C., Mason, H. D., Franks, S. & Holly, J. M. The insulin-like growth factors (IGFs) in follicular fluid are predominantly bound in the ternary complex. *J. Endocrinol.* **155**, R1–R4 (1997).
75. Khosravi, M. J., Diamandi, A., Mistry, J., Krishna, R. G. & Khare, A. Acid-labile subunit of human insulin-like growth factor-binding protein complex: measurement, molecular, and clinical evaluation. *J. Clin. Endocrinol. Metab.* **82**, 3944–3951 (1997).
76. Labarta, J. I. et al. Immunoblot studies of the acid-labile subunit (ALS) in biological fluids, normal human serum and in children with GH deficiency and GH receptor deficiency before and after long-term therapy with GH or IGF-I respectively. *Clin. Endocrinol.* **47**, 657–666 (1997).
77. Wandji, S. A., Gadsby, J. E., Simmen, F. A., Barber, J. A. & Hammond, J. M. Porcine ovarian cells express messenger ribonucleic acids for the acid-labile subunit and insulin-like growth factor binding protein-3 during follicular and luteal phases of the estrous cycle. *Endocrinology* **141**, 2638–2647 (2000).

78. Moon, J. S. & Choi, Y. H. Multiplex PCR for the rapid detection of insulin-like growth factor in the Pacific oyster, *Crassostrea gigas*: a useful indicator for growth assessment. *Mol. Biol. Rep.* **46**, 1023–1031 (2019).
79. Hetz, J. A. et al. Growth axis maturation is linked to nutrition, growth and developmental rate. *Mol. Cell Endocrinol.* **411**, 38–48 (2015).
80. Arquier, N. et al. *Drosophila* ALS regulates growth and metabolism through functional interaction with insulin-like peptides. *Cell Metab.* **7**, 333–338 (2008).
81. Ueki, I. et al. Inactivation of the acid labile subunit gene in mice results in mild retardation of postnatal growth despite profound disruptions in the circulating insulin-like growth factor system. *Proc. Natl Acad. Sci. USA* **97**, 6868–6873 (2000).
82. Yakar, S. et al. Circulating levels of IGF-1 directly regulate bone growth and density. *J. Clin. Invest.* **110**, 771–781 (2002).
83. Yakar, S. et al. The ternary IGF complex influences postnatal bone acquisition and the skeletal response to intermittent parathyroid hormone. *J. Endocrinol.* **189**, 289–299 (2006).
84. Fritton, J. C. et al. The insulin-like growth factor-1 binding protein acid-labile subunit alters mesenchymal stromal cell fate. *J. Biol. Chem.* **285**, 4709–4714 (2010).
85. Courtland, H. W. et al. Low levels of plasma IGF-1 inhibit intracortical bone remodeling during aging. *Age* **35**, 1691–1703 (2013).
86. Swindell, W. R. Gene expression profiling of long-lived dwarf mice: longevity-associated genes and relationships with diet, gender and aging. *BMC Genomics* **8**, 353 (2007).
87. Mariño, G. et al. Insulin-like growth factor 1 treatment extends longevity in a mouse model of human premature aging by restoring somatotroph axis function. *Proc. Natl Acad. Sci. USA* **107**, 16268–16273 (2010).
88. Kim, Y. W. et al. Harnessing the paradoxical phenotypes of APOE ε2 and APOE ε4 to identify genetic modifiers in Alzheimer's disease. *Alzheimers Dement.* **17**, 831–846 (2021).
89. Domené, H. M. et al. Deficiency of the circulating insulin-like growth factor system associated with inactivation of the acid-labile subunit gene. *N. Engl. J. Med.* **350**, 570–577 (2004).
90. Hwa, V. et al. Total absence of functional acid labile subunit, resulting in severe insulin-like growth factor deficiency and moderate growth failure. *J. Clin. Endocrinol. Metab.* **91**, 1826–1831 (2006).
91. Firth, S. M., Yan, X. & Baxter, R. C. D440N mutation in the acid-labile subunit of insulin-like growth factor complexes inhibits secretion and complex formation. *Mol. Endocrinol.* **25**, 307–314 (2011).
92. Domené, H. M. et al. Human acid-labile subunit deficiency: clinical, endocrine and metabolic consequences. *Horm. Res.* **72**, 129–141 (2009).
93. Fofanova-Gambetti, O. V. et al. Impact of heterozygosity for acid-labile subunit (IGFALS) gene mutations on stature: results from the international acid-labile subunit consortium. *J. Clin. Endocrinol. Metab.* **95**, 4184–4191 (2010).
94. van Duyvenvoorde, H. A. et al. Homozygous and heterozygous expression of a novel mutation of the acid-labile subunit. *Eur. J. Endocrinol.* **159**, 113–120 (2008).
95. Hess, O. et al. A novel mutation in IGFALS, c.380T>C (p.L127P), associated with short stature, delayed puberty, osteopenia and hyperinsulinaemia in two siblings: insights into the roles of insulin growth factor-1 (IGF1). *Clin. Endocrinol.* **79**, 838–844 (2013).
96. Domené, H. M. et al. Heterozygous IGFALS gene variants in idiopathic short stature and normal children: impact on height and the IGF system. *Horm. Res. Paediatr.* **80**, 413–423 (2013).
97. Işık, E. et al. Clinical and biochemical characteristics and bone mineral density of homozygous, compound heterozygous and heterozygous carriers of three novel IGFALS mutations. *Eur. J. Endocrinol.* **176**, 657–667 (2017).
98. Kumar, A. et al. Pathogenic/likely pathogenic variants in the SHOX, GHR and IGFALS genes among Indian children with idiopathic short stature. *J. Pediatr. Endocrinol. Metab.* **33**, 79–88 (2020).
99. Franzoni, A. et al. Novel IGFALS mutations with predicted pathogenetic effects by the analysis of AlphaFold structure. *Endocrine* **79**, 292–295 (2023).
100. Domené, S. & Domené, H. M. The role of acid-labile subunit (ALS) in the modulation of GH-IGF-I action. *Mol. Cell Endocrinol.* **518**, 111006 (2020).
101. Högler, W. et al. IGFALS gene dosage effects on serum IGF-I and glucose metabolism, body composition, bone growth in length and width, and the pharmacokinetics of recombinant human IGF-I administration. *J. Clin. Endocrinol. Metab.* **99**, E703–E712 (2014).
102. Grandone, A. et al. Clinical features of a new acid-labile subunit (IGFALS) heterozygous mutation: anthropometric and biochemical characterization and response to growth hormone administration. *Horm. Res. Paediatr.* **81**, 67–72 (2014).
103. Haluzik, M. et al. Insulin resistance in the liver-specific IGF-1 gene-deleted mouse is abrogated by deletion of the acid-labile subunit of the IGF-binding protein-3 complex: relative roles of growth hormone and IGF-1 in insulin resistance. *Diabetes* **52**, 2483–2489 (2003).
104. de Boer, H. et al. Monitoring of growth hormone replacement therapy in adults, based on measurement of serum markers. *J. Clin. Endocrinol. Metab.* **81**, 1371–1377 (1996).
105. Thorén, M. et al. Serum insulin-like growth factor I (IGF-I), IGF-binding protein-1 and -3, and the acid-labile subunit as serum markers of body composition during growth hormone (GH) therapy in adults with GH deficiency. *J. Clin. Endocrinol. Metab.* **82**, 223–228 (1997).
106. Drake, W. M. et al. Optimizing growth hormone replacement therapy by dose titration in hypopituitary adults. *J. Clin. Endocrinol. Metab.* **83**, 3913–3919 (1998).
107. Marzullo, P. et al. Usefulness of different biochemical markers of the insulin-like growth factor (IGF) family in diagnosing growth hormone excess and deficiency in adults. *J. Clin. Endocrinol. Metab.* **86**, 3001–3008 (2001).
108. Fukuda, I. et al. Acid-labile subunit in growth hormone excess and deficiency in adults: evaluation of its diagnostic value in comparison with insulin-like growth factor (IGF)-I and IGF-binding protein-3. *Endocr. J.* **49**, 379–386 (2002).
109. Barrios, V. et al. Diagnostic interest of acid-labile subunit measurement in relationship to other components of the IGF system in pediatric patients with growth or eating disorders. *Eur. J. Endocrinol.* **144**, 245–250 (2001).
110. Ertl, D. A. et al. Diagnostic value of serum acid-labile subunit alone and in combination with IGF-I and IGFBP-3 in the diagnosis of growth hormone deficiency. *Horm. Res. Paediatr.* **93**, 371–379 (2020).
111. Yuen, K. C. J. et al. Diagnosis and testing for growth hormone deficiency across the ages: a global view of the accuracy, caveats, and cut-offs for diagnosis. *Endocr. Connect.* **12**, e220504 (2023).
112. Arosio, M. et al. Diagnostic value of the acid-labile subunit in acromegaly: evaluation in comparison with insulin-like growth factor (IGF) I, and IGF-binding protein-1, -2, and -3. *J. Clin. Endocrinol. Metab.* **86**, 1091–1098 (2001).
113. Morrison, K. M., Wu, Z., Bidlingmaier, M. & Strasburger, C. J. Findings and theoretical considerations on the usefulness of the acid-labile subunit in the monitoring of acromegaly. *Growth Horm. IGF Res.* **11**, S61–S63 (2001).
114. Giustina, A. et al. Multidisciplinary management of acromegaly: a consensus. *Rev. Endocr. Metab. Disord.* **21**, 667–678 (2020).
115. Wallace, J. D. et al. Responses of the growth hormone (GH) and insulin-like growth factor axis to exercise, GH administration, and GH withdrawal in trained adult males: a potential test for GH abuse in sport. *J. Clin. Endocrinol. Metab.* **84**, 3591–3601 (1999).
116. Equey, T. et al. Application of the athlete biological passport approach to the detection of growth hormone doping. *J. Clin. Endocrinol. Metab.* **107**, 649–659 (2022).
117. Neumann, O. et al. Methylome analysis and integrative profiling of human HCCs identify novel protumorigenic factors. *Hepatology* **56**, 1817–1827 (2012).
118. Udali, S. et al. DNA methylation and gene expression profiles show novel regulatory pathways in hepatocellular carcinoma. *Clin. Epigenet.* **7**, 43 (2015).
119. Marquardt, J. U. et al. Sequential transcriptome analysis of human liver cancer indicates late stage acquisition of malignant traits. *J. Hepatol.* **60**, 346–353 (2014).
120. Yu, J., Zhang, H., Zhang, Y. & Zhang, X. Integrated analysis of the altered lncRNA, microRNA, and mRNA expression in HBV-positive hepatocellular carcinoma. *Life* **12**, 701 (2022).
121. Ge, S. et al. Identification of the diagnostic biomarker VIPR1 in hepatocellular carcinoma based on machine learning algorithm. *J. Oncol.* **2022**, 2469592 (2022).
122. Ye, J. et al. Prognosis-related molecular subtypes and immune features associated with hepatocellular carcinoma. *Cancers* **14**, 5721 (2022).
123. Huang, J. et al. Novel potential biomarkers for severe alcoholic liver disease. *Front. Immunol.* **13**, 1051353 (2022).
124. Mucci, L. A. et al. Plasma levels of acid-labile subunit, free insulin-like growth factor-I, and prostate cancer risk: a prospective study. *Cancer Epidemiol. Biomark. Prev.* **19**, 484–491 (2010).
125. Ma, C. et al. Circulating insulin-like growth factor 1-related biomarkers and risk of lethal prostate cancer. *JNCI Cancer Spectr.* **6**, pkab091 (2022).
126. Johansson, M. et al. Genetic and plasma variation of insulin-like growth factor binding proteins in relation to prostate cancer incidence and survival. *Prostate* **69**, 1281–1291 (2009).
127. Cao, Y. et al. Insulin-like growth factor pathway genetic polymorphisms, circulating IGF1 and IGFBP3, and prostate cancer survival. *J. Natl Cancer Inst.* **106**, dju085 (2014).
128. Chen, J. et al. High-resolution bisulfite-sequencing of peripheral blood DNA methylation in early-onset and familial risk breast cancer patients. *Clin. Cancer Res.* **25**, 5301–5314 (2019).
129. Wang, F., Tang, C., Gao, X. & Xu, J. Identification of a six-gene signature associated with tumor mutation burden for predicting prognosis in patients with invasive breast carcinoma. *Ann. Transl. Med.* **8**, 453 (2020).
130. Zhao, Y., Zhang, Y., Dai, C., Hong, K. & Guo, Y. A signature constructed with mitophagy-related genes to predict the prognosis and therapy response for breast cancer. *Aging* **14**, 6169–6186 (2022).
131. Canzian, F. et al. Polymorphisms of genes coding for insulin-like growth factor 1 and its major binding proteins, circulating levels of IGF-I and IGFBP-3 and breast cancer risk: results from the EPIC study. *Br. J. Cancer* **94**, 299–307 (2006).
132. Deming, S. L. et al. Genetic variation in IGF1, IGF-1R, IGFALS, and IGFBP3 in breast cancer survival among Chinese women: a report from the Shanghai Breast Cancer Study. *Breast Cancer Res. Treat.* **104**, 309–319 (2007).
133. Taverne, C. W. et al. Common genetic variation of insulin-like growth factor-binding protein 1 (IGFBP-1), IGFBP-3, and acid labile subunit in relation to serum IGF-I levels and mammographic density. *Breast Cancer Res. Treat.* **123**, 843–855 (2010).
134. Daughaday, W. H. & Trivedi, B. Measurement of derivatives of proinsulin-like growth factor-II in serum by a radioimmunoassay directed against the E-domain in normal subjects and patients with nonislet cell tumor hypoglycemia. *J. Clin. Endocrinol. Metab.* **75**, 110–115 (1992).
135. Zapf, J., Futo, E., Peter, M. & Froesch, E. R. Can 'big' insulin-like growth factor II in serum of tumor patients account for the development of extrapancreatic tumor hypoglycemia? *J. Clin. Invest.* **90**, 2574–2584 (1992).

136. Dynkevich, Y. et al. Tumors, IGF-2, and hypoglycemia: insights from the clinic, the laboratory, and the historical archive. *Endocr. Rev.* **34**, 798–826 (2013).
137. Baxter, R. C. & Daughaday, W. H. Impaired formation of the ternary insulin-like growth factor-binding protein complex in patients with hypoglycemia due to nonislet cell tumors. *J. Clin. Endocrinol. Metab.* **73**, 696–702 (1991).
138. Daughaday, W. H., Trivedi, B. & Baxter, R. C. Abnormal serum IGF-II transport in non-islet cell tumor hypoglycemia results from abnormalities of both IGF binding protein-3 and acid labile subunit and leads to elevation of serum free IGF-II. *Endocrine* **3**, 425–428 (1995).
139. Teale, J. D., Blum, W. F. & Marks, V. Alleviation of non-islet cell tumour hypoglycaemia by growth hormone therapy is associated with changes in IGF binding protein-3. *Ann. Clin. Biochem.* **29**, 314–323 (1992).
140. Baxter, R. C. et al. Regulation of the insulin-like growth factors and their binding proteins by glucocorticoid and growth hormone in nonislet cell tumor hypoglycemia. *J. Clin. Endocrinol. Metab.* **80**, 2700–2708 (1995).
141. Katz, L. E. et al. The effect of growth hormone treatment on the insulin-like growth factor axis in a child with nonislet cell tumor hypoglycemia. *J. Clin. Endocrinol. Metab.* **81**, 1141–1146 (1996).
142. Bond, J. J., Meka, S. & Baxter, R. C. Binding characteristics of pro-insulin-like growth factor-II from cancer patients: binary and ternary complex formation with IGF binding proteins-1 to -6. *J. Endocrinol.* **165**, 253–260 (2000).
143. Boisclair, Y. R., Wang, J., Shi, J., Hurst, K. R. & Ooi, G. T. Role of the suppressor of cytokine signaling-3 in mediating the inhibitory effects of interleukin-1beta on the growth hormone-dependent transcription of the acid-labile subunit gene in liver cells. *J. Biol. Chem.* **275**, 3841–3847 (2000).
144. Kong, S. E., Firth, S. M., Baxter, R. C. & Delhanty, P. J. Regulation of the acid-labile subunit in sustained endotoxemia. *Am. J. Physiol. Endocrinol. Metab.* **283**, E692–E701 (2002).
145. Baxter, R. C., Hawker, F. H., To, C., Stewart, P. M. & Holman, S. R. Thirty-day monitoring of insulin-like growth factors and their binding proteins in intensive care unit patients. *Growth Horm. IGF Res.* **8**, 455–463 (1998).
146. Van den Berghe, G. et al. A paradoxical gender dissociation within the growth hormone/insulin-like growth factor I axis during protracted critical illness. *J. Clin. Endocrinol. Metab.* **85**, 183–192 (2000).
147. Flannery, B. M., Amuzie, C. J. & Pestka, J. J. Evaluation of insulin-like growth factor acid-labile subunit as a potential biomarker of effect for deoxynivalenol-induced proinflammatory cytokine expression. *Toxicology* **304**, 192–198 (2013).
148. Ruiz-Sanmartín, A. et al. Characterization of a proteomic profile associated with organ dysfunction and mortality of sepsis and septic shock. *PLoS ONE* **17**, e0278708 (2022).
149. Salie, M. T. et al. Data-independent acquisition mass spectrometry in severe rheumatic heart disease (RHD) identifies a proteomic signature showing ongoing inflammation and effectively classifying RHD cases. *Clin. Proteom.* **19**, 7 (2022).
150. Xu, G. et al. Virus-inducible IGFALS facilitates innate immune responses by mediating IRAK1 and TRAF6 activation. *Cell Mol. Immunol.* **18**, 1587–1589 (2021).
151. Lee, J. S. et al. Longitudinal proteomic profiling provides insights into host response and proteome dynamics in COVID-19 progression. *Proteomics* **21**, e2000278 (2021).
152. Richard, V. R. et al. Early prediction of COVID-19 patient survival by targeted plasma multi-omics and machine learning. *Mol. Cell Proteom.* **21**, 100277 (2022).
153. Kimura, Y. et al. Identification of serum prognostic biomarkers of severe COVID-19 using a quantitative proteomic approach. *Sci. Rep.* **11**, 20638 (2021).
154. Völlmy, F. et al. A serum proteome signature to predict mortality in severe COVID-19 patients. *Life Sci. Alliance* **4**, e202101099 (2021).
155. Calvet, J. et al. Biomarker candidates for progression and clinical management of COVID-19 associated pneumonia at time of admission. *Sci. Rep.* **12**, 640 (2022).
156. Fischer, F. et al. Associations of insulin-like growth factors, insulin-like growth factor binding proteins and acid-labile subunit with coronary heart disease. *Clin. Endocrinol.* **61**, 595–602 (2004).
157. Prentice, R. L. et al. Novel proteins associated with risk for coronary heart disease or stroke among postmenopausal women identified by in-depth plasma proteome profiling. *Genome Med.* **2**, 48 (2010).
158. Chen, H. et al. Systemic biomarkers and unique pathways in different phenotypes of heart failure with preserved ejection fraction. *Biomolecules* **12**, 1419 (2022).
159. Heyse, W. et al. Identification of patient subtypes based on protein expression for prediction of heart failure after myocardial infarction. *iScience* **26**, 106171 (2023).
160. Wysokinski, W. E. et al. Impact of atrial fibrillation on platelet gene expression. *Eur. J. Haematol.* **98**, 615–621 (2017).
161. Bereket, A. et al. Regulation of the acid-labile subunit of the insulin-like growth factor ternary complex in patients with insulin-dependent diabetes mellitus and severe burns. *Clin. Endocrinol.* **44**, 525–532 (1996).
162. Lai, Y. C., Li, H. Y., Wu, T. J., Jeng, C. Y. & Chuang, L. M. Correlation of circulating acid-labile subunit levels with insulin sensitivity and serum LDL cholesterol in patients with type 2 diabetes: findings from a prospective study with rosiglitazone. *PPAR Res.* **2014**, 917823 (2014).
163. Kershaw, N. J. et al. SOCS3 binds specific receptor-JAK complexes to control cytokine signaling by direct kinase inhibition. *Nat. Struct. Mol. Biol.* **20**, 469–476 (2013).
164. Woolson, H. D., Thomson, V. S., Rutherford, C., Yarwood, S. J. & Palmer, T. M. Selective inhibition of cytokine-activated extracellular signal-regulated kinase by cyclic AMP via Epac1-dependent induction of suppressor of cytokine signalling-3. *Cell Signal.* **21**, 1706–1715 (2009).
165. Cocolakis, E. et al. Smad signaling antagonizes STAT5-mediated gene transcription and mammary epithelial cell differentiation. *J. Biol. Chem.* **283**, 1293–1307 (2008).
166. Bianchi, M., Meng, C. & Ivashkiv, L. B. Inhibition of IL-2-induced Jak-STAT signaling by glucocorticoids. *Proc. Natl Acad. Sci. USA* **97**, 9573–9578 (2000).
167. Wei, S. & Qiu, Y. MiR-210-5p regulates STAT3 activation by targeting STAT5A in the differentiation of dermal fibroblasts. *3 Biotech* **11**, 243 (2021).
168. D'Alessandro, A. et al. Serum proteomics in COVID-19 patients: altered coagulation and complement status as a function of IL-6 level. *J. Proteome Res.* **19**, 4417–4427 (2020).

Competing interests

The author declares no competing interests.

Additional information

Peer review information *Nature Reviews Endocrinology* thanks Horacio Domene, Briony Forbes and Shoshana Yakar for their contribution to the peer review of this work.

Related links

Human Gene Mutation Database: www.hgmd.cf.ac.uk
The Human Protein Atlas: www.proteinatlas.org/