

Potential Role of mTORC1 in Linking Amino-Acid Availability, GH-IGF-1 Signaling, and Growth-Plate Function in Childhood Stunting: A Narrative Review

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ABSTRACT

Stunting affects 150.2 million children under five worldwide. Its mechanism is frequently explained by caloric deficiency alone. The mechanistic target of rapamycin complex 1 (mTORC1) pathway has emerged as a biochemical link between dietary amino acid availability and the hormonal signaling that drives linear bone growth. This review examines the potential relationships among mTORC1 signaling, the growth hormone–insulin-like growth factor 1 (GH-IGF-1) axis, growth-plate chondrocytes, and environmental enteric dysfunction (EED) in childhood stunting. A literature search was done through PubMed and Google Scholar using combinations of the terms "mTORC1," "stunting," "essential amino acids," "IGF-1," "growth plate," "chondrocyte," and "environmental enteric dysfunction". Essential amino acids, particularly leucine, activate mTORC1 through Rag GTPase and Ragulator sensing. mTORC1 activity, in turn, supports hepatic IGF-1 synthesis and directly regulates growth plate chondrocyte proliferation and differentiation through the S6K1-Gli2-PTHrP axis. Independently, chronic infection and EED trigger systemic inflammation that inhibits IGF-1 synthesis through a diet-independent route, converging on the same downstream growth signaling pathway. The mTORC1 pathway provides an explanation of how dietary protein quality and infection burden determines linear growth outcomes, with potential implications for how complementary feeding and infection control are prioritized in stunting prevention programs. Further studies are needed to clarify how these pathways interact and whether mTORC1 represents a direct causal link between nutritional and inflammatory determinants of stunting.

Keywords: mTORC1; child stunting; IGF-1; growth plate; environmental enteric dysfunction

INTRODUCTION

Stunting is defined by the World Health Organization (WHO) as a length- or height-for-age z-score more than two standard deviations below the median of the WHO Child Growth Standards. It affects an estimated 150.2 million children under five globally, with high prevalence across South and Southeast Asia and sub-Saharan Africa [1]. Individually, stunted children face elevated risks of impaired cognitive development, reduced educational attainment, and, in adulthood, higher susceptibility to metabolic disease [2].

Public health initiatives to address stunting have centered on total caloric and micronutrient adequacy. The results of that approach have been mixed, raising a question of whether a pathomechanism besides raw energy intake is being missed [3]. A specific pathway involves protein quality rather than quantity, which is a single intracellular signaling hub of the mechanistic target of rapamycin complex 1, or mTORC1.

mTORC1 is a serine/threonine kinase complex that functions as a central intracellular integrator of nutrient and growth-factor signals, integrating amino acid availability, cellular energy status, oxygen tension, and growth factor signaling to regulate anabolic processes including protein synthesis and cell growth [4,5]. mTORC1 activity is particularly sensitive to essential amino acid availability. It regulates the GH-IGF-1 axis and growth plate chondrocyte behavior. This finding has emerged as a plausible biochemical connection between dietary intake and linear growth [6].

This review traces that connection in three stages: essential amino acid activation of mTORC1, mTORC1's integration with the GH-IGF-1 axis and growth plate chondrogenesis, and the independent suppression of this same axis by chronic infection and environmental enteric dysfunction (EED). This pathway was chosen because it follows the pathway of the actual biochemical sequence from dietary input to skeletal outcome. We also aim to explain the reasons behind infection as a determinant factor of stunting besides dietary measures.

METHODS

This is a narrative review; thus, no formal protocol was registered, and no PRISMA methodology was applied. Literature published between 2010 to 2026 was identified through targeted searches of PubMed and Google Scholar using combinations of the terms "mTORC1," "stunting," "essential amino acids," "IGF-1," "growth plate," "chondrocyte," and "environmental enteric dysfunction." Priority was given to human clinical and cohort studies where available. Murine mechanistic studies were included where they

provided the only available evidence for a specific molecular mechanism. Sources were selected based on their mechanistic relevance, and when conflicting findings existed between studies, both were reported for a more comprehensive discussion.

DISCUSSION

Essential Amino Acids and mTORC1 Activation

mTORC1 is sensitive to a small subset of essential amino acids, of which leucine is the most extensively characterized [7]. Leucine level is detected through a sensing cascade involving intracellular sensors that converge on the Rag GTPase complex. Active Rag GTPases recruit mTORC1 to the lysosomal surface via the Ragulator complex, where it is activated by the GTPase Rheb. GTPase Rheb is then controlled by the tuberous sclerosis complex (TSC1/TSC2) in response to growth factor signaling [8,9].

A study involving stunted Malawian children reported significantly lower serum concentrations of all essential amino acids, including leucine, isoleucine, and valine, compared with non-stunted children (<0.01) [6]. This finding is difficult to measure solely with the caloric model of stunting, since children in the same food-insecurity setting differed specifically in the amino acid profile most relevant to mTORC1 activation. Diets built predominantly around starchy staples can meet caloric targets while remaining relatively poor in the specific essential amino acids that most efficiently activate mTORC1. Animal-source foods (ASF) contain these amino acids at considerably higher density and bioavailability than most plant sources [10,11].

TABLE 1: mTORC1 Pathway Components and Their Role in Linear Growth.

Component	Type	Role in mTORC1-growth signaling	Reference
Leucine/branched-chain amino acids	Substrate	Primary amino acid input sensed upstream of mTORC1 activation	[7]
Rag GTPases-Ragulator	Sensing complex	Recruits mTORC1 to the lysosomal surface in response to amino acid sufficiency	[8]
TSC1/TSC2	Negative regulator	Inhibits Rheb, restraining mTORC1 activation until growth factor signals are present	[9]
IGF-1	GH/IGF-1 effector	Mediator between systemic and local growth-promoting effects of GH and contributes to growth-plate activity	[11]
S6K1 - Gli2 - PTHrP	Downstream effector axis	Local chondrocyte signaling cascade pacing proliferation versus premature differentiation	[13]

mTORC1, GH-IGF-1 Axis, and Growth Plate Chondrogenesis

Several molecular mechanisms may link mTORC1 signaling to linear growth (Table 1). Once activated, mTORC1 does not act on bone growth directly but through its integration with the GH-IGF-1 axis (Figure 1).

Chronic undernutrition is proven to induce acquired GH resistance, in which circulating GH remains normal or elevated but hepatic IGF-1 output falls [10]. Nutritional status influences hepatic IGF-1 production. mTORC1 functions as a nutrient-sensitive regulator of growth and protein synthesis.

It also acts locally within growth plate chondrocytes as a direct proliferative signal, independent of circulating IGF-1 [12]. A study in murine models has shown that mTORC1 deletion in chondrocytes reduces extracellular matrix synthesis and delays chondrocyte hypertrophy, producing measurable deficits in bone elongation. Conversely, the activation of mTORC1 through deletion of its negative regulator TSC1 was reported by one group to disrupt the normal proliferation-differentiation sequence, producing disorganized growth plate architecture [13]. A subsequent independent

replication using a comparable genetic strategy found more limited effects confined to the resting zone, with no measurable change in chondrocyte proliferation or hypertrophy [14]. This discrepancy indicates that the precise phenotypic consequences of mTORC1 dysregulation in growth plate chondrocytes are not yet fully resolved. mTORC1 downstream kinase S6K1 phosphorylates the transcription factor Gli2, promoting transcription of parathyroid hormone-related peptide (PTHrP), which maintains chondrocyte proliferation and delays premature hypertrophic differentiation [13].

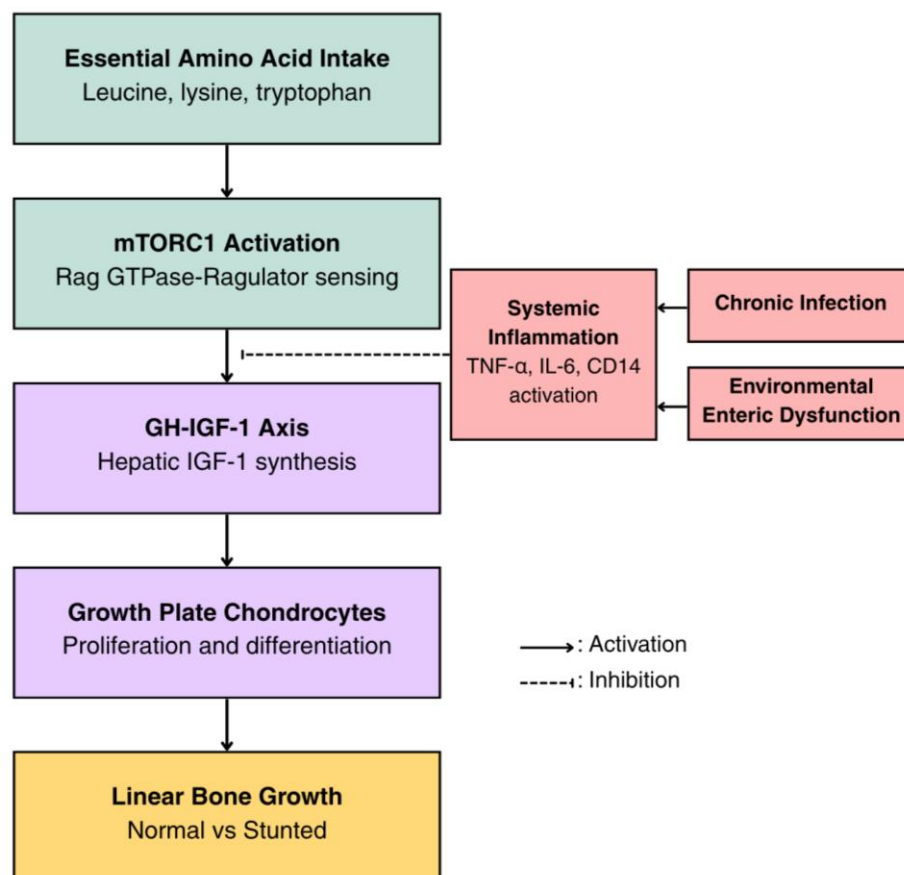


FIGURE 1: Flowchart of the mTORC1 pathway linking diet and infection to child stunting.

The Connection Between Infection, Environmental Enteric Dysfunction, and Independent Suppression of Growth Signaling

Among scientific studies, factors of infectious disease burden and complete basic immunization are often reported as having a stronger correlation with growth outcomes than dietary intake alone. This is consistent with a mechanism of chronic low-grade inflammation, which most often originates from environmental enteric dysfunction (EED). It is an acquired subclinical enteropathy of the small intestine characterized by villous blunting, crypt hyperplasia, and increased intestinal permeability [15]. A systematic review of EED biomarker studies found consistent support for an association between intestinal inflammation, systemic inflammation, and stunting [16,18].

Translocated bacterial products activate innate immune signaling, which produces sustained elevation of pro-inflammatory cytokines that directly suppress hepatic IGF-1 synthesis and induce growth hormone resistance, independent of dietary amino acid supply [17]. An Indonesian birth cohort longitudinal study among infants followed from six to twelve months of age showed that elevated EED biomarkers were present in over 80% of the cohort. A pathway analysis showed that a marker of systemic monocyte activation (CD14) was negatively associated with plasma IGF-1, which was in turn a significant determinant of length-for-age z-score at twelve months [18]. The key human and mechanistic evidence supporting the proposed relationships between amino acid availability, mTORC1 signaling, EED, IGF-1, and growth-plate function is summarized in Table 2.

TABLE 2: Evidence Supporting the mTORC1-GH-IGF-1-Growth Plate Pathway.

Evidence	Study type	Main finding	Reference
Circulating essential amino acids and stunting	Human, cross-sectional	Stunted children had significantly lower serum essential amino acids, independent of energy intake	[6]
Chondrocyte TSC1 deletion (mTORC1 hyperactivation)	Animal, murine	Disorganized growth plate architecture and disrupted proliferation-differentiation coupling	[13]
Chondrocyte TSC1 deletion, replication	Animal, murine	Effects confined to resting zone only; no change in proliferation or hypertrophy	[14]
EED biomarkers, systemic inflammation, and IGF-1	Human, longitudinal cohort	CD14 negatively associated with IGF-1 in which IGF-1 is a significant determinant of LAZ at 12 months	[18]

LIMITATIONS

An important limitation concerns causal direction in the level of epidemiological evidence. Most field data connecting infection burden, feeding practices, and stunting outcomes are observational and cross-sectional. A longitudinal study is needed to prove that suppressed mTORC1 signaling is the mechanism connecting infection to growth faltering, as opposed to some other pathway, or that infection and growth faltering are jointly caused by an unmeasured third factor such as household socioeconomic status. At the current state of evidence, the mTORC1 framework is best understood as a biologically plausible and increasingly well-supported hypothesis that unifies several previously disparate observations, rather than as a fully proven causal pathway.

CLINICAL IMPLICATIONS

Nutritional dietary recommendations among children should incorporate protein quality indicators besides only feeding frequency, since a child fed at recommended frequency with a diet low in animal-source protein could still experience chronic mTORC1 under activation. Similarly, infection control and immunization completion should be considered as growth interventions, given that inflammation appears to suppress IGF-1 output through a route that operates largely independently of dietary intake. These implications should be read as hypotheses for further investigation. In order to prove its causality, further studies should apply intervention designs capable of separating the effects of protein quality from total caloric intake and infection control from nutritional supplementation.

CONCLUSIONS

The mTORC1 pathway offers an explanation of how dietary amino acid quality and infection burden could converge on a single pathway to determine linear growth outcomes in children. Evidence supporting individual links in this chain is backed by human clinical or cohort data, although important pieces, including the precise phenotypic consequences of chondrocyte mTORC1 dysregulation, remain unresolved.

The framework provides a mechanistic hypothesis in the linkage of nutritional and inflammatory exposures to impaired linear growth. Future studies are needed to further explain protein quality, caloric adequacy, and infection burden as the factors determining stunting.

DECLARATIONS

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Conflicts of Interest: The authors declare no conflict of interest.

Ethics Statement: N/A; This study is a narrative literature review; no original human or animal data were collected.

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