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SUPPLEMENTARY MATERIALS

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MICROBIOME

Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition

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In most animal species, juvenile growth is marked by an exponential gain in body weight and size. Here we show that the microbiota of infant mice sustains both weight gain and longitudinal growth when mice are fed a standard laboratory mouse diet or a nutritionally depleted diet. We found that the intestinal microbiota interacts with the somatotropic hormone axis to drive systemic growth. Using monocolonized mouse models, we showed that selected lactobacilli promoted juvenile growth in a strain-dependent manner that recapitulated the microbiota's effect on growth and the somatotropic axis. These findings show that the host's microbiota supports juvenile growth. Moreover, we discovered that lactobacilli strains buffered the adverse effects of chronic undernutrition on the postnatal growth of germ-free mice.

During the juvenile growth period, the gain in animal body size varies widely as a result of the interactions between nutritional input and the organism's hormonal cues. In mammals, postnatal growth is controlled by the activity of the somatotropic axis (fig. S1), in which growth hormone (GH) instructs the liver and peripheral tissues to produce insulin-like growth factor–1 (IGF-1), to promote organ and systemic growth (*1*–*3*). Chronic undernutrition triggers a state of GH resistance (*4*, *5*) that leads to stunting, and juveniles become small and thin (*6*). Acute malnutrition, in contrast, causes wasting, defined as severe weight loss and mediated in part through the disruption of the gut microbiota (*7*). However, the contribution of the gut microbiota to normal postnatal growth and its influence on the activity of the somatotropic axis during chronic undernutrition remain unknown.

To address this question, we first compared the growth parameters of wild-type (WT) and germ-free (GF) infant male mice fed a standard breeding diet (25% proteins, 9% fats; table S1) until young adulthood (8 weeks old, Fig. 1 and fig. S2). After weaning, the GF and WT animals ingested similar amounts of food relative to body weight (fig. S3), yet at 8 weeks of age, GF mice weighed 14.5% less and were 4% shorter than WT mice (Fig. 1, A and C; fig. S2, A and B; and table S2). These growth differences were most pronounced after weaning (Fig. 1, A to D, and fig. S2, C and D). Thus, with a standard breeding diet, the gut microbiota ensures optimal weight gain and longitudinal growth, especially around weaning. Remarkably, the 17% weight gain seen in WT animals (fig. S2A and table S2) was not a consequence of increased adiposity. The epididymal fat pads and adipocyte size of WT and GF males remained similar (fig. S4, A to D). Likewise, levels of leptin, a circulating marker of fat stores (*8*), were similar in the sera of WT and GF animals (fig. S4E). However, the weight gain of the organs of WT animals was greater than that of GF mice (fig. S2E and table S2), confirming that a WT microbiota is associated with optimal systemic somatic growth. This contrasts with the increased adiposity that results from subtherapeutic antibiotic treatments in infant mice that is apparently caused by disrupting the gut microbiota community (*9*, *10*). WT animals were 4% longer (fig. S2B and table S2), indicating that the microbiota also influences skeletal growth. Bone growth parameters, including femur length, cortical thickness, cortical bone fraction, and the trabecular fraction of the femur (Fig. 1, E and F; fig. S2, F to I; and table S2) were all reduced in GF animals, although cortical bone mineral density (BMD) was unaffected (fig. S2J). Previously, Sjögren *et al.* showed that trabecular BMD was increased in GF animals relative to their WT siblings (*11*). However, that study was conducted on females of a different genetic background than ours. Nevertheless, taken together, our results show that the gut microbiota sustains postnatal somatic tissue growth, leading to increased mass gain and enhanced longitudinal growth.

Postnatal systemic growth is mainly driven by the activity of the somatotropic axis (*1*–*3*), where the pituitary gland produces GH, which induces the production of IGF-1. The liver is the major source of circulating IGF-1 and together with IGF-1 binding protein-3 (IGFBP-3) serves as an endocrine determinant of somatic growth (*3*, *12*, *13*) (fig. S1). In addition, IGF-1 is produced by peripheral tissues, including muscles, and acts to promote tissue growth in an autocrine/paracrine manner

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(*14*) (fig. S1). We therefore measured circulating levels of GH and IGF-1, the major components of this axis (*3*, *15*, *16*), in the sera of WT and GF animals. GH levels peaked around birth and gradually declined during postnatal growth in both WT and GF animals (Fig. 2A). IGF-1 titers were significantly reduced in GF animals (Fig. 2B), as were the circulating levels of IGFBP-3 in sera (*17*) (Fig. 2C). In addition, *Igf1* expression was reduced in muscles of GF animals at both 28 and 56 days (fig. S5, A and B). In the liver, both *Igf1* and *Igfbp3* expression were reduced in GF mice at 28 days (Fig. 2, D and E), at the same time that IGF-1 circulating titers peaked in WT animals (Fig. 2B). Likewise, the phosphorylation of Akt at Ser 473 (phospho-S473-Akt), a marker of IGF-1 receptor (IGF-1R) signaling activity (*18*) (fig. S1), was reduced in the liver of GF animals as compared to WT animals both at 28 (Fig. 2F) and 56 days (fig. S5C).

To assess the importance of IGF-1 levels in mediating postnatal growth dynamics, we repeatedly injected GF and WT animals with recombinant IGF-1 (rIGF-1) for 10 days after weaning and analyzed their growth parameters. GF animals significantly increased their weight, as well as body and femur length, over the treatment period (fig. S5, D to G). Injections of rIGF-1 into WT animals did not promote growth (fig. S5, D to F), even though they modulated two established markers of IGF-1 activity: reduced glycemia and increased phospho-S473-Akt signals in the liver (fig. S5, H and I). In GF mice, IGF-1 levels in sera were reduced compared to those in WT mice despite normal circulating GH levels, and an exogenous supply of rIGF-1 was sufficient to enhance growth to levels seen in WT animals (fig. S5, D, E, and G). We thus concluded that the microbiota promoted growth by facilitating IGF-1 production and activity. To further test this hypothesis, we treated WT animals with the cyclolignan compound picropodophyllin (PPP), a specific noncompetitive inhibitor of IGF-1R (*19*, *20*), for 10 days. The PPP treatment significantly retarded the growth gains expected of WT animals (Fig. 4, D to F) and decreased the rIGF-1–mediated impact on phospho-S473-Akt signals in the liver and glycemia dynamics (fig. S8, J and K). These results established that IGF-1 activity is necessary for growth in WT animals. Together, our data show that the gut microbiota influences the production and activity of IGF-1 required for postnatal growth.

We then tested the effects of chronic undernutrition on, and the contribution of the gut microbiota to, postnatal growth. To this end, we weaned GF and WT juveniles onto a nutritionally depleted diet low in proteins (8.6%), fats (2.4%), and vitamins (table S1) and monitored their growth until 8 weeks of age (Fig. 3). During the week of adaptation to solid food, both GF and

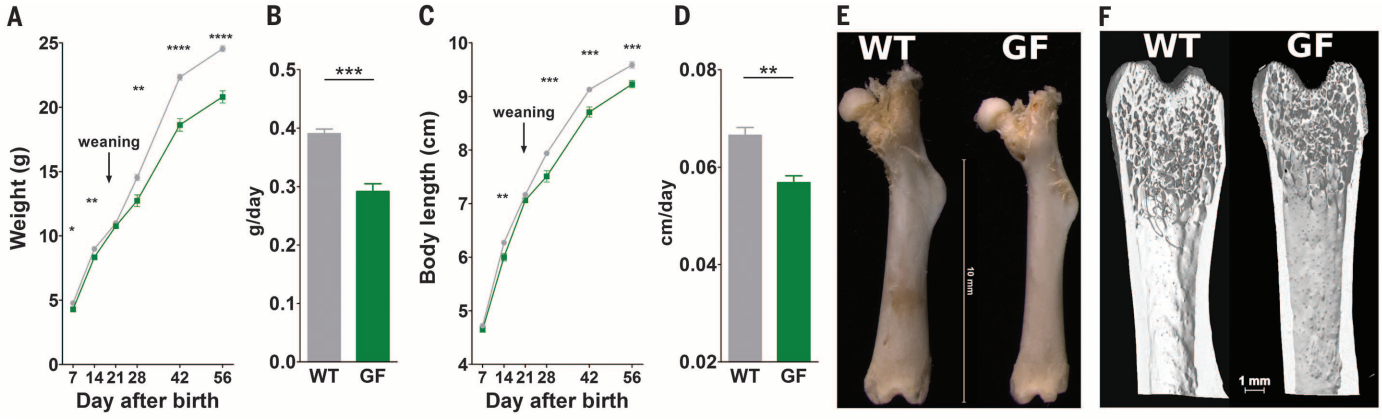

Fig. 1. The microbiota maintains mouse juvenile growth. (**A** to **D**) Weight (A) and body length (C) growth curves during the juvenile period (day 7 to day 56 after birth) and daily weight (B) and body size (D) gains after weaning (day 21 to day 56) of WT (gray) (n = 16) and GF (green) (n = 12) infant male mice bred with their mothers from birth until day 21, weaned, and then fed a breeding diet from 21 to 56 days old. (**E**) Photograph of representative femur bones at day 56. (**F**) Three-dimensional reconstructions of representative distal parts of femur bones at day 56. Error bars indicate SEM. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

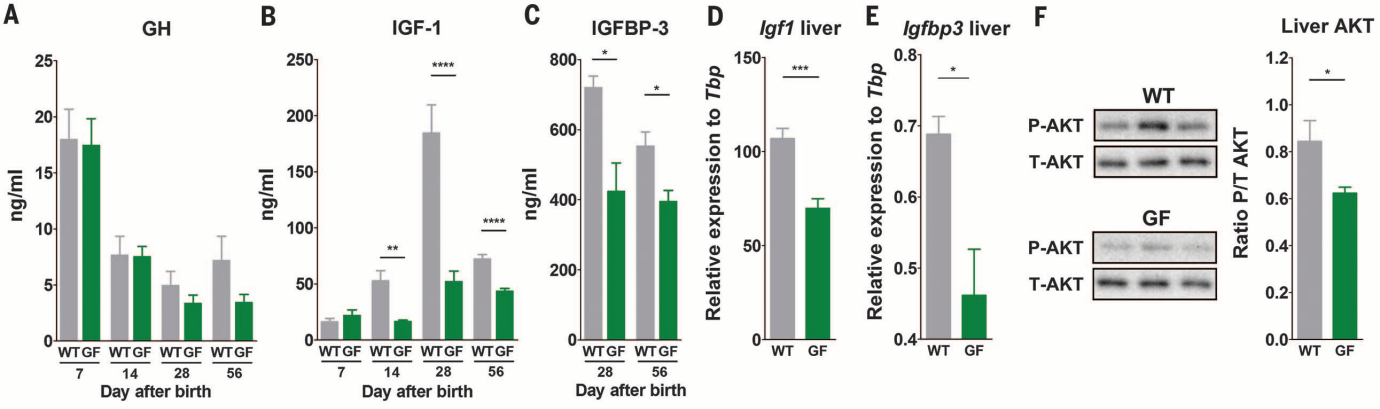

Fig. 2. The microbiota maintains systemic somatotropic axis activity. (**A** to **C**) Levels of GH (A), IGF-1 (B), and IGFBP-3 (C) in sera of WT (gray) and GF (green) mice at given time points after birth, $n \geq 5$ mice per group. (**D** to **F**) Expression levels of *Igf1* (D) and *Igfbp3* in liver (E) at day 28 after birth (n = 5 or 6 mice per group). (F) Western blots and quantification of phospho-S473-Akt in liver of WT and GF mice (n = 5 or 6 mice per group) at day 28 after birth . Representative blots of three mice per group are shown. Data are presented as means ± SEM. *P < 0.05, ***P < 0.001, ****P < 0.0001.

WT animals lost weight, yet weight loss was more extensive in GF animals (fig. S6C). After adaptation to solid food, the growth of GF animals was arrested, whereas WT animals resumed growth and recovered weight and longitudinal growth (Fig. 3, A to C, and fig. S6, A to E), albeit to a lesser extent than those on the breeding diet. The stunted phenotype of GF animals was not the result of an alteration of the GF animals' food intake relative to their body weight (fig. S7, A to D) nor of an altered capacity to absorb energy from the diet (fig. S7E). We conclude therefore that the gut microbiota contributes to maintaining mouse juvenile growth during chronic undernutrition.

We then analyzed how the gut microbiota influences the somatotropic axis during undernutrition (Fig. 4). We quantified GH, IGF-1, and IGFBP-3 levels in GF and WT animals after weaning onto the depleted diet. At 28 days, GH levels were elevated in GF animals as compared with WT animals, whereas at 56 days, GF animals displayed reduced circulating levels of GH, similar to WT animals (Fig. 4A). In contrast to WT animals, both IGF-1 and IGFBP-3 circulating levels failed to peak at 56 days in GF animals (Fig. 4, B and C). In muscle at 28 days (7 days after weaning onto the depleted diet), the expression of both *GH-receptor* (*Ghr*) and *Igf1* in WT animals was elevated compared to that in GF animals (fig. S8, A and B). Further, *Socs3*, a transcriptional target of GHR signaling (*21*) (fig. S1), was also increased in WT muscles (fig. S8C). In the liver at 28 days, *Ghr* expression was increased in WT animals as compared with GF counterparts (fig. S8D). At 56 days, circulating titers of IGF-1 (Fig. 4B), along with *Igf1* expression in the muscles and liver (fig. S8, E and F), increased; *Igfbp3* and *Socs3* expression (fig. S8, G and H) and the phospho-S473-Akt signal were also increased in the liver of WT animals (fig. S8I). Collectively, these results indicate a reduced activity of the somatotropic axis in GF animals. Next, we repeatedly injected 28-day-old WT animals weaned on the depleted diet with the PPP compound for 10 days and monitored their growth. We observed that PPP-treated animals had reduced weight, body length, and femur length gains over the treatment period as compared with untreated mice (Fig. 4, D to G). Taken together, these results indicate that during undernutrition, the gut microbiota helps to maintain systemic somatotropic axis activity and that this activity does result in some postnatal growth.

We have previously showed that gut microbiota promote *Drosophila* juvenile growth during undernutrition (*22*). Furthermore, monoassociation of GF *Drosophila* with selected lactobacilli strains recapitulates the growth promotion seen when a more complex microbiota is present (*22*). Lactobacilli strains are commensal in a variety of animals, including *Drosophila* and mammals (*23*, *24*). These taxa also share evolutionarily conserved nutrient-sensing endocrine pathways that regulate juvenile growth (i.e, *Drosophila* insulin/IGF-like peptides and mammalian IGFs) (*25*). We thus tested the functional potential of specific lactobacilli strains on murine juvenile growth and

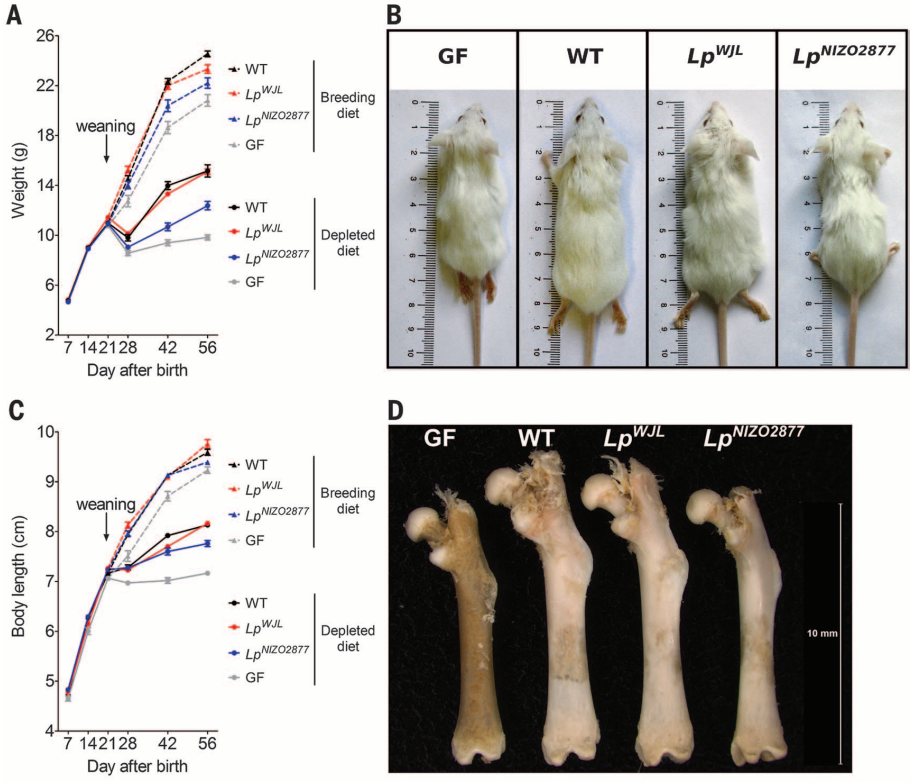

Fig. 3. The microbiota and a *L. plantarum* strain maintain mouse juvenile growth upon undernutrition. (**A** to **C**) Weight (A) and body length (C) growth curves of WT (n = 12 and 15, black lines), GF (n = 12 and 20, gray lines), Lp^{WJL} (n = 8 and 28, red line), and $Lp^{NIZO2877}$ (n = 12 and 15, blue line) monocolonized male mice on breeding (triangles and dashed lines) or nutritionally depleted (circles and solid lines) diets. (B) Representative photographs of mice on depleted diet at day 56 after birth. (**D**). Photographs of representative femur bones at day 56 after birth of GF, WT, Lp^{WJL}-, and $Lp^{NIZO2877}$-associated mice raised on the depleted diet.

the somatotropic axis during undernutrition. Two *Lactobacillus plantarum* strains that display different growth-promoting capacities in *Drosophila* monocolonized models were selected for monoassociation experiments in GF mice. Using monocolonized *Drosophila*, we identified *L. plantarum*^{WJL} (Lp^{WJL}) as a potent growth promoter, whereas *L. plantarum*^{NIZO2877} ($Lp^{NIZO2877}$) showed a statistically less pronounced effect on *Drosophila* growth (fig. S9). We then monitored postnatal growth of monocolonized infant male mice with Lp^{WJL} and $Lp^{NIZO2877}$ strains. These mice were obtained after monocolonizing GF adult mice of both sexes with the Lp^{WJL} or $Lp^{NIZO2877}$ strains; monocolonized adults were mated 20 days after colonization, and groups of six offspring were nursed by their monocolonized dam and naturally colonized by the respective *Lactobacillus* strain acquired from the dam. Lactating mice and their pups were maintained on the breeding diet. Twenty-one days after birth, the juveniles were weaned on either the breeding or the depleted diet (fig. S10). On the depleted diet, although both Lp^{WJL} and $Lp^{NIZO2877}$ juveniles gained more weight (+52% and +27% respectively; Fig. 3, A and B; fig. S6, A to D; and table S2) and body length (+14% and +8% respectively; Fig. 3, B and C; fig. S6E; and table S2) as compared with GF animals, the Lp^{WJL}-associated animals grew better (+25% weight and +6% length) than $Lp^{NIZO2877}$-associated animals (Fig. 3, A to C, and fig. S6, A to E). The quantitative difference between the two strains was not a result of differences in food intake relative to body weight (fig. S7, A to D), differential capacity to absorb energy from the diet (fig. S7E), or a marked difference in the efficiency of bacterial colonization of the intestinal tract (fig. S7, F to H). Lp^{WJL}-colonized animals showed a 14% body length gain when compared to GF animals, whereas $Lp^{NIZO2877}$-associated animals gained only 8% (fig. S6E and table S2). Similarly, bone growth such as femur length was differentially affected (Fig. 3D, fig. S6F, and table S2), indicating that the growth benefit depends on the strain of *L. plantarum*. In terms of weight gain, on the depleted diet, WT animals were 53% heavier than GF animals (fig. S6D and table S2). Lp^{WJL}-colonized animals showed a 52% weight gain, whereas $Lp^{NIZO2877}$-associated animals only showed 27% weight gain (fig. S6D and table S2). A similar effect was observed in all organs tested (fig. S6, G to J, and table S2). Collectively, the data show that during postnatal growth, selected lactobacilli strains can recapitulate the effect of a WT microbiota on mouse juvenile growth that would otherwise be stunted

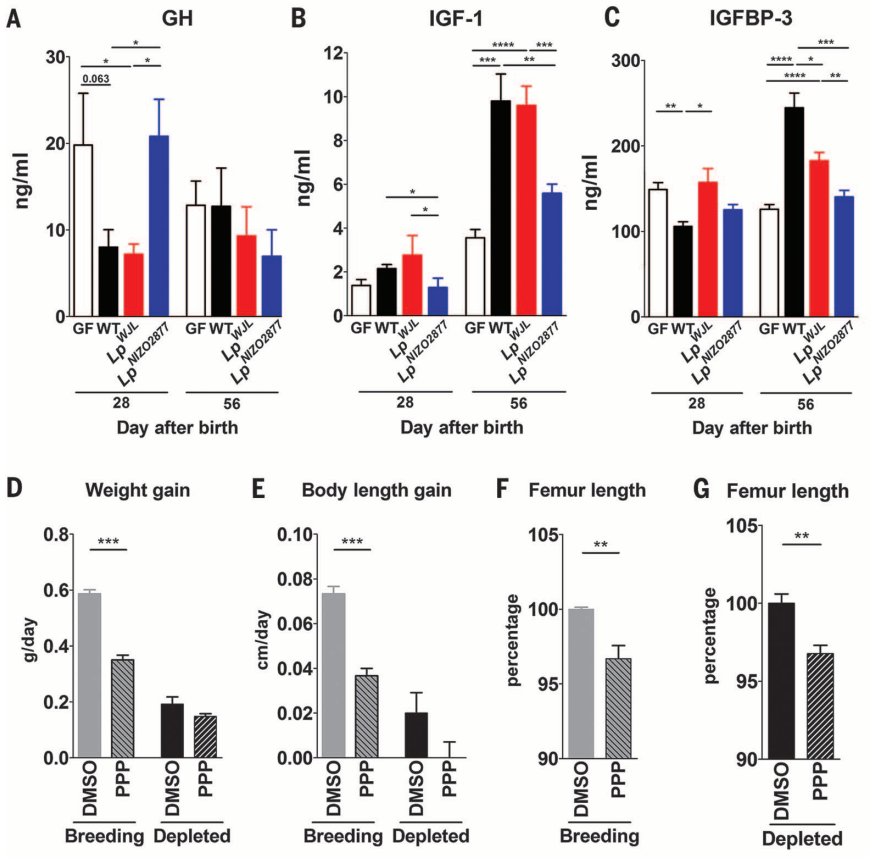

Fig. 4. The microbiota and a *L. plantarum* strain maintain somatotropic axis activity upon undernutrition. (**A** to **C**) Levels of GH (A), IGF-1 (B), and IGFBP-3 (C) in sera of GF (white), WT (black), Lp^{WJL}- (red), and $Lp^{NIZO2877}$-(blue) colonized mice at day 28 (n = 5 or 6 mice per group) and day 56 ($n \geq 15$ mice per group) after birth. (**D** to **G**) Weight gain (D), body length gain (E), and femur length [(F) and (G)] of WT mice weaned at day 21 on the breeding (gray bars) or depleted (black bars) diets and treated with DMSO or the IGF-1R inhibitor PPP (cross-hatched bars) for 10 days (n = 3 or 4 mice per group). Data are presented as means ± SEM. $^{**}P < 0.01$, $^{***}P < 0.001$.

by undernutrition. Strain-dependent promotion of juvenile growth and IGF-1 titers were not restricted to undernourished mice but were also observed with those fed the breeding diet (Fig. 3, A to C, and fig. S6, A to F, and K).

We observed that Lp^{WJL}- and $Lp^{NIZO2877}$-colonized animals differed in their ability to sustain somatotropic axis activity. Lp^{WJL}-colonized mice largely recapitulated the growth features of WT animals, but $Lp^{NIZO2877}$-colonized animals had either an intermediate or similar response to that of the GF animals (Fig. 4, A to C). By 56 days, the GH titers of WT animals fed on the depleted diet were comparable to those observed in WT animals raised on the breeding diet. However, the IGF-1 titers of these mice had dwindled by more than sevenfold (compare Fig. 2, A and B, and Fig. 4, A and B), confirming that chronic undernutrition affects the activity of the GH/IGF-1 axis (*4*). Furthermore, although GH titers of GF and $Lp^{NIZO2877}$-associated animals at 28 days were elevated, they failed to elicit adequate tissue responses, implying that the activity of the somatotropic axis is impaired in GF juveniles and that their tissues are in a state of GH resistance. We hypothesized that reduced GH sensitivity is less severe in WT and Lp^{WJL}-associated animals but remains in $Lp^{NIZO2877}$-associated animals. To directly test this hypothesis, we injected 28–day-old GF, WT, Lp^{WJL}-, and $Lp^{NIZO2877}$-associated animals weaned on the depleted diet with recombinant GH (rGH) and assayed the activation of the GHR signaling pathway in their liver. We examined the phosphorylation of Tyr^{694} of STAT5a and Tyr^{699} of STAT5b, which are direct signatures of GHR signaling activity (*26*, *27*) (fig. S11). GF and $Lp^{NIZO2877}$-colonized animals were less sensitive to rGH injection than WT and Lp^{WJL}-colonized animals (fig. S11). Our data showed that the microbiota is necessary and that a selected lactobacillus strain is sufficient to partly abrogate the GH resistance of peripheral tissues caused by chronic undernutrition.

Our study shows that GF infant mice enter a GH-resistant state upon chronic undernutrition, and a WT microbiota is necessary and sufficient to boost postnatal growth by enhancing GH sensitivity and thereby increasing IGF-1 activity in peripheral tissues. In addition, this study establishes that a selected strain of *L. plantarum* can recapitulate the beneficial effects of the microbiota on the somatotropic axis and on mouse juvenile growth, a functionality that may be shared with other commensal bacteria in the microbiota. We envision that, together with nutritional therapy, microbial interventions using selected bacterial strains may represent a novel and complementary strategy to buffer the adverse effects of chronic undernutrition on human postnatal growth, which still affects more than 160 million of children below 5 years of age in low- and middle-income countries (*28*).

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SUPPLEMENTARY MATERIALS

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Tables S1 and S2
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Science

Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition

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Microbiota and infant development

Malnutrition in children is a persistent challenge that is not always remedied by improvements in nutrition. This is because a characteristic community of gut microbes seems to mediate some of the pathology. Human gut microbes can be transplanted effectively into germ-free mice to recapitulate their associated phenotypes. Using this model, Blanton *et al.* found that the microbiota of healthy children relieved the harmful effects on growth caused by the microbiota of malnourished children. In infant mammals, chronic undernutrition results in growth hormone resistance and stunting. In mice, Schwarzer *et al.* showed that strains of *Lactobacillus plantarum* in the gut microbiota sustained growth hormone activity via signaling pathways in the liver, thus overcoming growth hormone resistance. Together these studies reveal that specific beneficial microbes could potentially be exploited to resolve undernutrition syndromes.

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