Rewiring of Uric Acid Metabolism in the Intestine Promotes High-Altitude Hypoxia Adaptation in Humans

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Abstract

Adaptation to high-altitude hypoxia is characterized by systemic and organ-specific metabolic changes. This study investigates whether intestinal metabolic rewiring is a contributing factor to hypoxia adaptation. We conducted a longitudinal analysis over 108 days, with seven time points, examining fecal metabolomic data from a cohort of 46 healthy male adults traveling from Chongqing (a.s.l. 243 m) to Lhasa (a.s.l. 3,658 m) and back. Our findings reveal that short-term hypoxia exposure significantly alters intestinal metabolic pathways, particularly those involving purines, pyrimidines, and amino acids. A notable observation was the significantly reduced level of intestinal uric acid, the end product of purine metabolism, during acclimatization (also called acclimation) and additional two long-term exposed cohorts (Han Chinese and Tibetans) residing in Shigatse, Xizang (a.s.l. 4,700 m), suggesting that low intestinal uric acid levels facilitate adaptation to high-altitude hypoxia. Integrative analyses with gut metagenomic data showed consistent trends in intestinal uric acid levels and the abundance of key uric acid-degrading bacteria, predominantly from the Lachnospiraceae family. The sustained high abundance of these bacteria in the long-term resident cohorts underscores their essential role in maintaining low intestinal uric acid levels. Collectively, these findings suggest that the rewiring of intestinal uric acid metabolism, potentially orchestrated by gut bacteria, is crucial for enhancing human resilience and adaptability in extreme environments.

Key words: **high-altitude hypoxia, intestinal UA, metabolic rewiring, UA-degrading bacteria, human acclimatization.**

Discoveries

Introduction

The challenge of high-altitude hypoxia presents a unique opportunity to observe the remarkable adaptability of human metabolism. The metabolic rewiring at both systemic and organ levels has been documented to confer significant benefits during hypoxia adaptation (Matheson et al. 1991; Baibas et al. 2005; Castillo et al. 2007). Native Tibetans, residing at elevations exceeding 3,000 m, demonstrate distinctive physiological adaptations (Zhou et al. 2023), such as stable glucose homeostasis (Braun 2008; Woolcott et al. 2015),

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reduced oxidative stress (Quindry et al. 2016; Horscroft et al. 2017), low cardiovascular disease mortality (Faeh et al. 2009), and fortified intestinal barrier function (McKenna et al. 2022), collectively mitigating the risks of metabolic syndrome in high-altitude hypoxic conditions. Adaptation extends beyond the respiratory, cardiovascular, and hematological systems, which adjust to ensure a continuous oxygen supply to metabolic tissues (Ramirez et al. 2007; Storz et al. 2010). In skeletal muscle, adaptation manifests as a rewiring of the tricarboxylic acid cycle (TCA) (Capitanio et al. 2017), while in the liver, it involves a shift in tryptophan metabolism, decreasing kynurenine synthesis in favor of tryptamine production (Mohapatra et al. 2021). These examples underscore the critical role of metabolic rewiring in systemic and organ-level adaptation to hypoxia (Midha et al. 2023). Yet, the intestinal metabolic rewiring and its role in promoting hypoxia acclimatization/adaptation remain largely unexplored.

The intestine, as a core metabolic site, plays an indispensable role in human adaptation to high-altitude environments by ensuring the integrity of the barrier and metabolic homeostasis. High-altitude–induced systemic hypoxia can precipitate ischemia of the intestinal mucosa, compromise the intestinal barrier, and disrupt the gut microbiota balance, leading to metabolic disorders (Suzuki et al. 2019). Consequently, individuals ascending to high altitudes frequently encounter gastrointestinal issues such as anorexia, abdominal discomfort, indigestion, acid reflux, and infectious diarrhea (Adak et al. 2014), which can exacerbate the risk of altitude-related diseases (Karl et al. 2018; McKenna et al. 2022).

In light of these challenges, our study analyzed fecal metabolomic data from 46 participants over seven time points to reveal the metabolic rewiring in the intestine triggered by systemic hypoxia. Our findings indicate that (i) hypoxia exposure significantly alters fecal metabolites and various metabolic pathways, including those of nucleotides (including purines and pyrimidines) and amino acids, with purine metabolism showing a particularly strong signal. (ii) The end product of purine metabolism, uric acid (UA), increased initially but declined during later exposure stages. Observations in additional cohorts, including six long-term Han Chinese populations (~5 to 60 months) and native Tibetans living at high altitudes (Shigatse, Xizang, a.s.l. 4,700 m), consistently showed intestinal UA levels below detection thresholds. This consistent pattern indicates that lower intestinal UA concentrations may be advantageous for physiological adaptation to high-altitude hypoxia. (iii) Through gut metagenomic data analysis targeting UA gene clusters, we identified a notable presence of UA-degrading bacteria within both short-term and long-term Han Chinese cohorts, as well as native Tibetans. These bacteria, largely from the Lachnospiraceae family, increased in abundance under hypoxia exposure, a trend that paralleled the changes in intestinal UA levels. Our findings reveal that intestinal metabolism, particularly UA metabolism, undergoes adaptive rewiring likely driven by gut bacteria, thereby facilitating human acclimatization/adaptation to high-altitude hypoxia.

Results

Significant Alterations in Fecal Metabolites Occurred with High-Altitude Hypoxia Exposure

We collected 260 fecal samples at seven distinct time points from 46 participants who transitioned from the lowland plains (a.s.l. 243 m) to the Qinghai–Tibet Plateau (a.s.l. 3,658 m), where they spent 73 days. Subsequently, 20 participants returned to the lowland areas, as illustrated in Fig. 1a.

To minimize the confounding influences of diet and lifestyle on our findings, we employed rigorous controls: Participants refrained from antibiotic use for at least 1 month and ceased probiotic product intake 2 weeks prior to the initial sampling (CQ1, control group). Meals were standardized across participants, provided in a unified canteen, and consisted of traditional Chinese cuisine, including rice, vegetables, and meat, with alcohol consumption prohibited. Additionally, participants shared uniform accommodation and maintained comparable daily routines. Subsequently, our metabolomic data yielded an abundance profile of 2,612 metabolites. After applying quality control protocols outlined in the Materials and Methods, 2,311 metabolites were retained for in-depth study.

Partial least-squares discriminant analysis (*PLS-DA*) indicated that high-altitude hypoxia significantly influenced the fecal metabolite profile (PERMANOVA $P = 0.001$; Fig. 1b). The distinct separation of the LS2 time point from others suggests a substantial correlation between fecal metabolites and hypoxia exposure, independent of potential dietary changes postarrival at high altitude. To further explore the dynamics of fecal metabolites under hypoxia, 190 significantly differential fecal metabolites (SDFMs) [fold change > 1, variable importance in projection (VIP) > 1, false discovery rate (FDR) < 0.2] were categorized into four clusters based on their longitudinal trajectories (Fig. 1c; supplementary fig. S1 and table S1, Supplementary Material online). Some metabolites exhibited initially upregulated (LS1 and LS2) followed by a recovery trend (from LS3-CQ3) (Cluster 1), while others increased during initial exposure (LS1) and continued to fluctuate (since LS2) (Cluster 2). The remaining metabolites remained stable during exposure and surged upon return to lowland (Cluster 3) or consistently decreased from the onset of exposure (Cluster 4). The majority of fecal metabolites (65.2%) fell into Cluster 1 ($n = 77$, 40.5%) and Cluster 2 ($n = 47$, 24.7%), indicating a clear influence of hypoxia exposure on fecal metabolite dynamics.

The SDFMs Were Enriched Mainly in Purine, Pyrimidine, and Amino Acid Metabolism Pathways

To elucidate the metabolic pathways that are altered under hypoxic conditions, enrichment analysis was performed utilizing the SDFMs (Fig. 2; supplementary table S2, Supplementary Material online). Our analysis revealed significant enrichment of SDFMs within nucleotide metabolism pathways (including purine and pyrimidine metabolism), amino acid metabolism

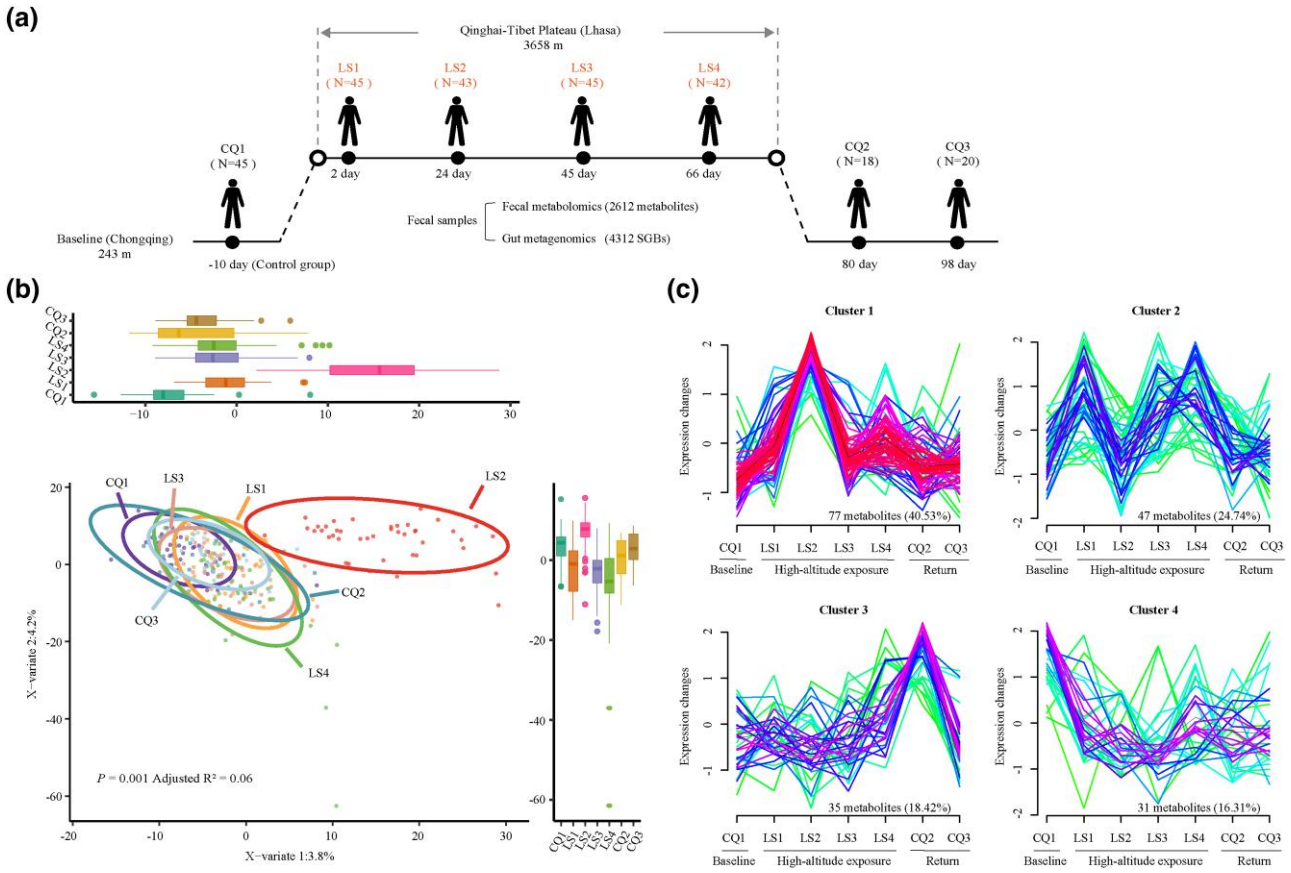

Fig. 1. Study design and fecal metabolite dynamics during high-altitude hypoxia. a) Diagrammatic representation of the study design, illustrating exposure to high-altitude hypoxia and the ensuing comprehensive longitudinal analysis of fecal metabolomics and metagenomics. b) *PLS-DA* score plot of 2311 identified fecal metabolites from 260 samples. Each point denotes an individual sample, with color coding reflecting different time points, and coordinates values for each sample at each time point depicted in boxplots. c) Cluster analysis of 190 significant fecal metabolites (fold change > 1, VIP > 1, FDR < 0.2), illustrating their temporal patterns associated with hypoxic exposure.

(such as histidine metabolism, arginine biosynthesis, and the metabolism of alanine, aspartate, and glutamate), and carbohydrate metabolism (FDR < 0.05). Notably, upon descent to lowland conditions (CQ3), these pathways continued to show significant enrichment (FDR < 0.05) compared to the baseline, particularly in pyrimidine metabolism and amino acid metabolism. These persistent modifications suggest a potential biological significance in the acclimatization to hypoxic environments.

Pathways demonstrating significant enrichment (FDR < 0.05) across at least two exposure time points were indicative of robust alterations under hypoxia (Butterfield et al. 2006; Torres et al. 2020). Our study identified 14 such metabolic pathways and 64 metabolites from the SDFMs (supplementary table S3, Supplementary Material online). Remarkably, three organic acids (fumarate, oxoglutaric acid, and pyruvate), and several amino acids, such as L-glutamine and glycine, were involved in a broad spectrum of metabolic pathways, encompassing both amino acid and nucleotide metabolism.

Significant shifts in fecal metabolites related to purine, pyrimidine, and amino acid metabolism primarily occurred during the exposure period (supplementary figs. S2 and S3 and table S2, Supplementary Material online). A total of 40 metabolites within these pathways demonstrated a high degree of consistency across individuals, particularly LS2 (Fig. 3). Within purine metabolism, metabolites such as urate (also known as UA), hypoxanthine, xanthosine, and xanthine were categorized under Cluster 1, while deoxyinosine and deoxyadenosine were in Cluster 2 and adenosine in Cluster 3. In pyrimidine metabolism, uracil, orotate, and pseudouridine were in Cluster 1, while deoxyuridine, thymidine, and thymine in Cluster 2 and deoxycytidine in Cluster 3. In amino acid metabolism, the majority of metabolites, including nine amino acids (L-glutamine, D-aspartic acid, L-aspartate, L-methionine, L-phenylalanine, L-serine, L-lysine, glycine, and citrulline) were in Cluster 1, with only L-tyrosine in Cluster 4. The trajectories of three key organic acids (fumarate, oxoglutaric acid, and pyruvate) were also in Cluster 1 (supplementary table S1, Supplementary Material online).

Overall, during the exposure period, the majority of metabolites were enriched in the three pathways: those involved in purine and pyrimidine metabolism were mainly in Cluster 1 or 2 (12/14), while amino acids and organic acids were predominantly in Cluster 1 (11/12). These findings suggest that the alterations of 40 core metabolites in these pathways occur predominantly during the early stages of exposure, as evidenced by the rapid increase from LS1 to LS2.

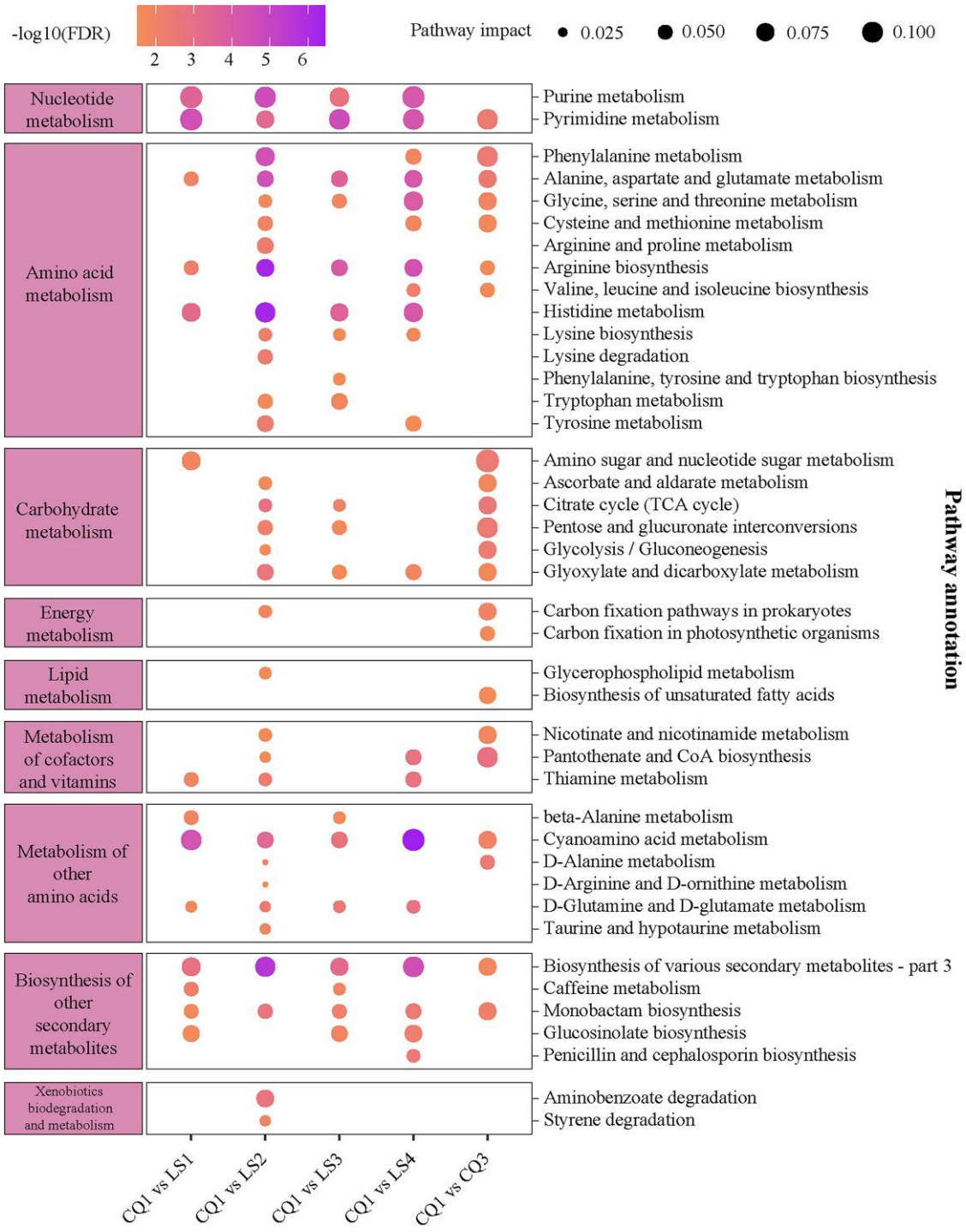

Fig. 2. KEGG pathway-based functional profiling of fecal metabolites. A bubble plot illustrates the significantly enriched KEGG pathways at various time points. The CQ2 time point is omitted due to the absence of significant pathway enrichment compared to the baseline. The left and right panels categorize the pathways according to KEGG metabolic categories: Levels B and C, respectively. In the central panel, bubble colors indicate the significance of enrichment relative to the baseline, while bubble sizes reflect the proportion of metabolites associated with each pathway. Enrichment significance (FDR) is calculated using Fisher's exact test (see "Materials and Methods").

Lower Levels of Intestinal UA Were Observed in Cohorts with Short-Term or Long-Term Exposure to High-Altitude Hypoxia

Our pathway enrichment analysis indicated significant alterations in metabolic pathways when compared to baseline levels under hypoxic conditions. Specifically, purine metabolism, pyrimidine metabolism, and cyanoamino acid (other amino acids) metabolism pathways showed the most substantial enrichment (pathway impact score > 0.1 and FDR < 0.001). Purine metabolism, in particular, was consistently upregulated across all four exposure time points (FDR < 0.05; supplementary table S2,

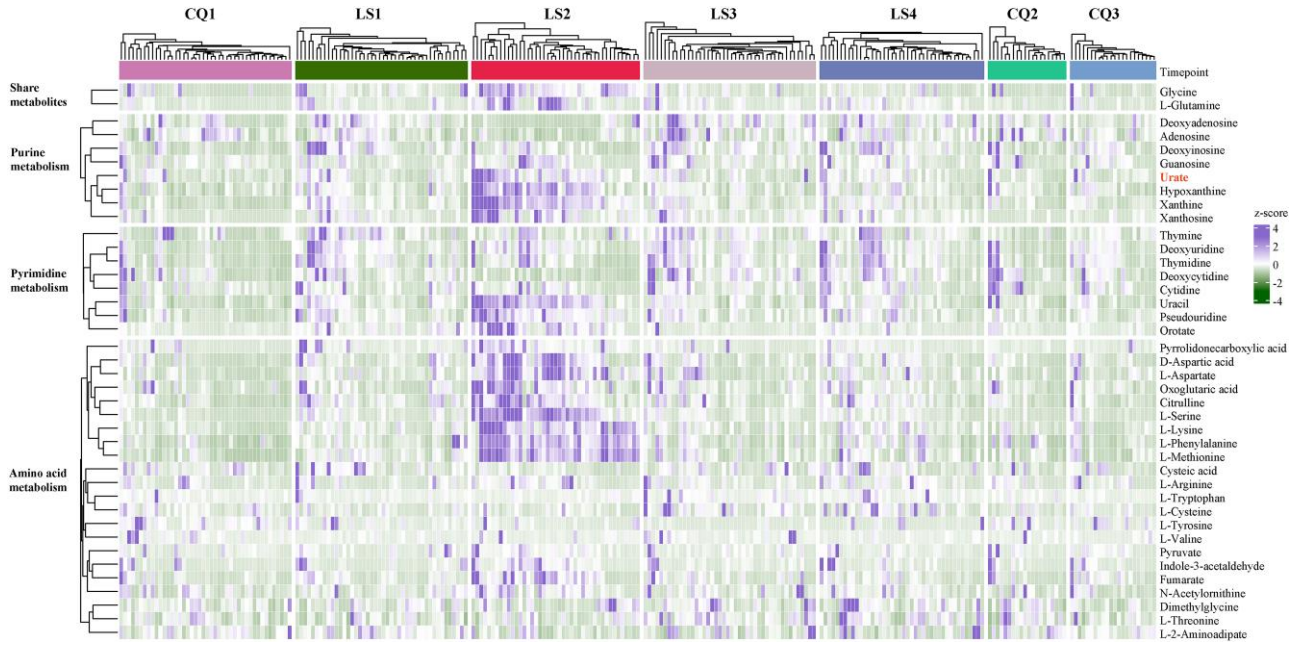

Fig. 3. Core metabolites dynamics under high-altitude hypoxia. This heatmap illustrates the longitudinal trajectory of key metabolites implicated in purine, pyrimidine, and amino acid metabolism, which are pivotal for high-altitude adaptation in humans. The left panel categorizes the pathways (Level B) enriched by these 40 notable metabolites. In the central panel, each grid corresponds to the relative abundance of a specific metabolite within a given sample, with the grid color denoting the *z*-score of the metabolite's relative abundance. On the right-hand panel, there corresponds a name for each metabolite. For additional insights, refer to supplementary figs. S2 and S3 and table S7, Supplementary Material online.

Supplementary Material online), with the highest pathway impact values observed at LS1 and LS4. These findings imply a critical role for intestinal purine metabolism in the physiological alterations under hypoxia and in facilitating adaptability to high-altitude conditions.

In line with these findings, we noted an initial increase in the abundance of UA, at LS2, followed by a reduction to baseline levels at LS3 and LS4 within our short-term exposure cohort. This pattern suggests the importance of maintaining low intestinal UA levels during later stages of exposure as the host acclimates to high-altitude hypoxia. Further validation was sought through nontargeted fecal metabolomic data from long-term exposure cohorts, including 163 Han residents (residing at high altitudes for above 5 to 60 months) and 28 native Tibetans from Shigatse, Xizang (a.s.l. 4,700 m). Remarkably, both cohorts displayed intestinal UA levels below the detection threshold, indicating a near absence of UA among long-term residents and natives adapted to high-altitude living. These results underscore the potential adaptive advantage of low intestinal UA levels under chronic high-altitude hypoxic conditions.

Lower Intestinal UA Levels Significantly Correlated with the Degradation of Gut Bacteria

Recent research has pinpointed a key gene cluster in gut bacteria crucial for degrading UA, thereby regulating UA levels in the host's intestine and blood (Kasahara et al. 2023; Liu, Xu, et al. 2023; Liu, Jarman, et al. 2023). Our study sought to detect this gene cluster in our cohorts, examining its link to intestinal UA levels under hypoxic conditions.

Analysis revealed 71 gene clusters spanning 5 phyla, 11 families, and 33 genera (Fig. 4a; supplementary table S4, Supplementary Material online). The Lachnospiraceae family within Firmicutes A was notably prevalent, representing 49.2% across seven time points (Fig. 5, Panel 1), with the *Blautia A* and *Enterocloster* genera each contributing 14%. Extending this analysis to 163 fecal metagenomic samples from six long-term exposure cohorts in Shigatse, Xizang (a.s.l. 4,700 m), we predicted 153 UA gene clusters (supplementary table S5, Supplementary Material online). Lachnospiraceae was again the most prominent family, particularly the *Collinsella* (17.6%), *Blautia A* (10.4%), and *Enterocloster* (7.1%) genera (supplementary fig. S4, Supplementary Material online). These patterns suggest a potential role for Lachnospiraceae in modulating intestinal UA levels under hypoxic stress.

Then, we quantified the total abundance of five UA-inducible genes, observing a significant increase in three at LS2 (Fig. 4b). Notably, the UA-degrading bacteria count was significantly higher only at LS2 (Fig. 4c). Further analysis revealed a significant positive correlation between purine-enriched metabolites and 71 UA-degrading bacteria, predominantly Lachnospiraceae, at LS2 (Fig. 5, Panel 2; supplementary fig. S5, Supplementary Material online). Concurrently, fecal UA levels reached the peaks at this time point, coinciding with a marked increase in indicator SGBs with UA gene clusters (Fisher's exact test, $P < 0.05$), comprising over 10% of the bacterial abundance

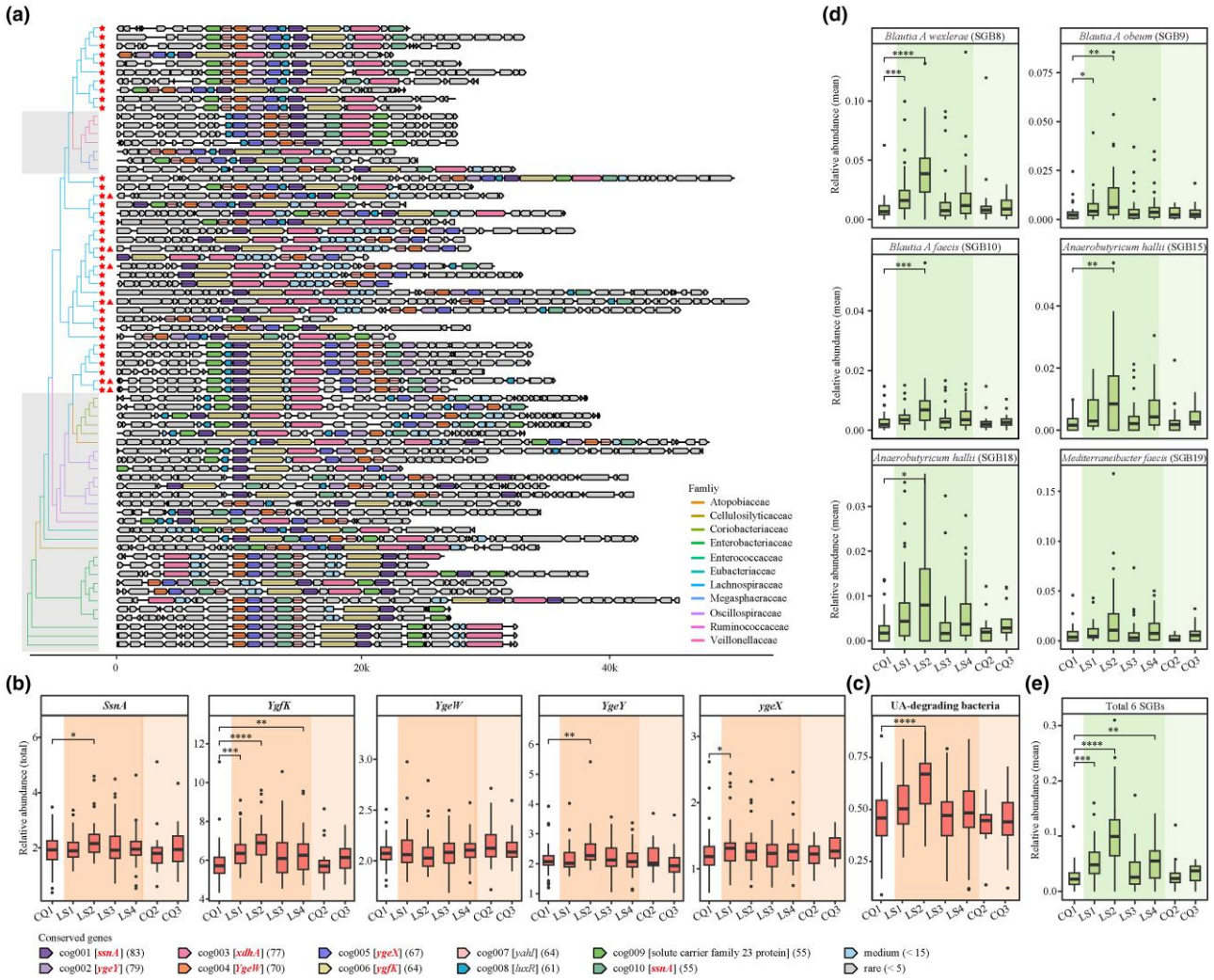

Fig. 4. Characteristics of UA gene cluster. a) The phylogenetic landscape of the UA gene cluster is depicted, with asterisks denoting SGBs from the Lachnospiraceae family and triangles highlighting the six indicator species in d). The shaded gray region delineates families distinct from Lachnospiraceae. See also supplementary table S4, Supplementary Material online. The term "cog" symbolizes the cluster orthogroup, with gene symbol IDs encased in square brackets. IDs highlighted in bold italic font signify UA-inducible genes validated by prior studies (Kasahara et al. 2023; Liu, Xu, et al. 2023; Liu, Jarman, et al. 2023), while the remaining IDs pertain to genes identified in our present study. Numbers in parentheses indicate the frequency of each gene within its respective cluster orthogroup. b) The total relative abundance of five UA-inducible genes in each sample, based on 1,079 SGBs. UA-inducible genes are styled in italicized text. Each point corresponds to an individual sample, with color gradients reflecting distinct exposure stages. c) The total abundance changes of UA-degrading bacteria in each sample. Here, "UA-degrading bacteria" refers to bacteria that harbor all five UA-inducible genes. d, e) The dynamic shifts in the relative abundance of the six indicator SGBs at the LS2 time point and their cumulative relative abundances, respectively. Statistical significance is denoted as follows: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ by Wilcoxon rank-sum test.

(Fig. 4d and e; supplementary table S6, Supplementary Material online). This trend suggests that UA may encourage the growth of UA-degrading bacteria, supporting their role in UA regulation, particularly in the initial 2 weeks of hypoxic exposure.

Discussion

This study deciphers the rewiring of intestinal metabolism in lowlanders during high-altitude hypoxia, focusing on its association with the host's adaptability to hypoxia. Short-term hypoxia exposure induced significant metabolic shifts in purine, pyrimidine, and amino acid pathways (hallmarks of hypoxia). These changes peak early (LS1-LS2) and then return to baseline, indicating a rapid initial impact on fecal metabolites followed by a recovery stage. This suggests that gut metabolism is regulated in response to high-altitude hypoxia, highlighting the intestine's essential role in maintaining cellular function and ensuring host survival in such conditions (Rocchetti et al. 2022; Zhao et al. 2023). Notably, the increase of multiple amino acids may protect cells from the challenge of hypoxia (Weinberg et al. 2016), like L-glutamine protects against hypoxia stress (Weinberg et al. 2016) and supports the intestinal barrier (Dos et al. 2020; Schumacher et al. 2021), vital for physiological and immunological functions, and

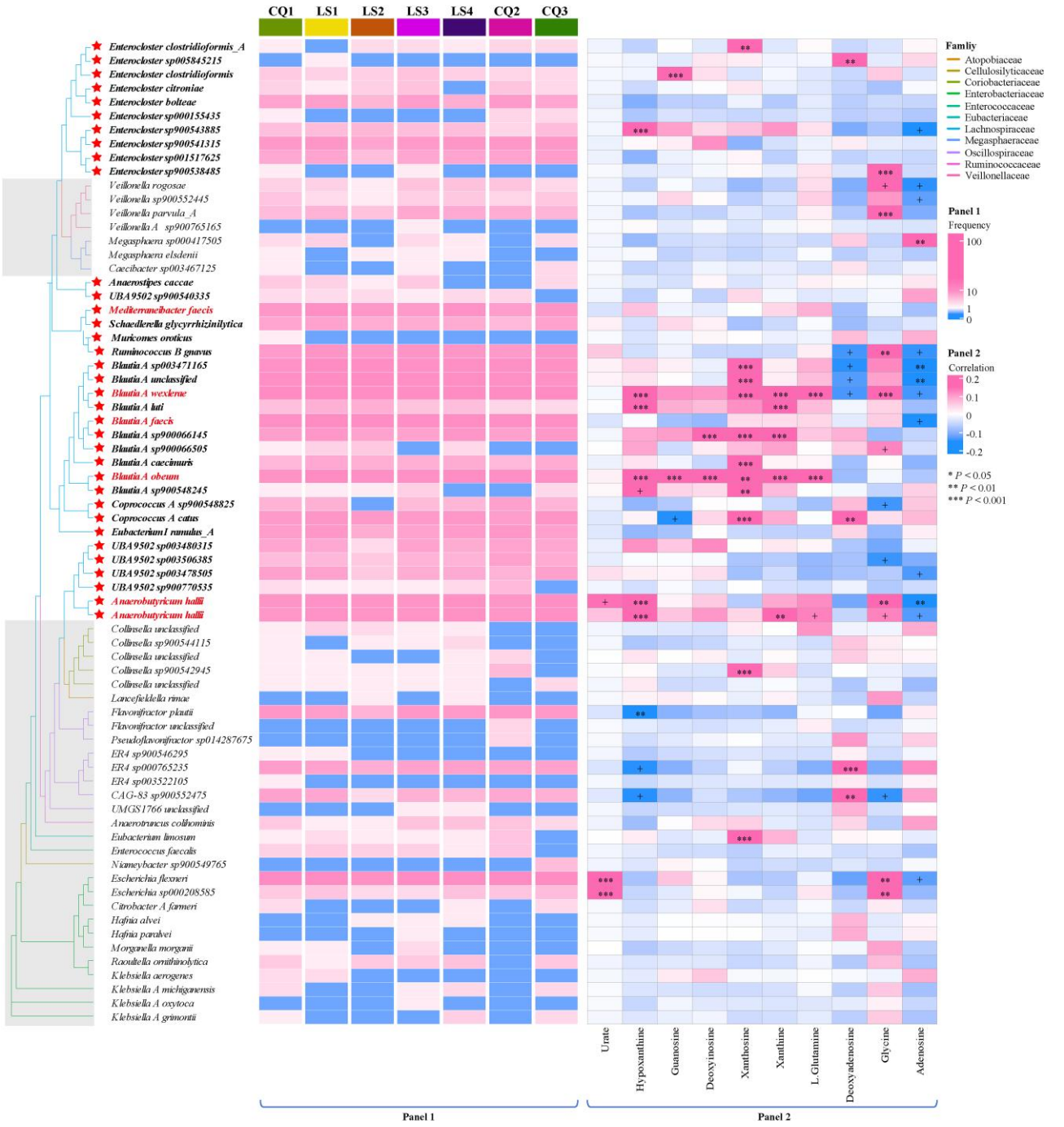

Fig. 5. Gene clusters from Lachnospiraceae exhibit the most stable and abundant capacity for UA consumption. Panel 1: Gene clusters from the Lachnospiraceae family demonstrate a significant and consistent capacity for UA consumption. The asterisk on the left highlights SGBs belonging to the Lachnospiraceae family. The red font emphasizes the six indicator species outlined in Fig. 4. The squares represent the prevalence of UA gene clusters across individuals at sequential time points, with frequencies above ten highlighted in the same color. Panel 2: Spearman's correlation coefficients detail the relationships between the relative abundance of SGBs, where the gene clusters are sourced, and ten fecal metabolites linked to purine metabolism. Correlations with absolute values exceeding 0.2 are indicated in the same color. Statistical significance is denoted as follows: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

microbial diversity (Xu et al. 2014). Similarly, glycine can protect cell function during hypoxia (Weinberg et al. 2016). Phenylalanine helps establish effective energy metabolism (Lin et al. 2016) and promote lung function under hypoxic conditions (Førli et al. 2000). Moreover, the conversion of amino acid and pyrimidine end-products into TCA cycle intermediates like fumarate, oxoglutaric acid, and pyruvate boosts energy metabolism, crucial for host endurance in high altitudes (Rocchetti et al. 2022; Zhao et al. 2023).

Purine metabolism, in particular, displayed a pronounced enrichment during hypoxia exposure. Intestinal UA, its end

product, showed a significant initial increase followed by a return to baseline levels in individuals exposed to short-term hypoxia. Intriguingly, populations long resident at high altitudes, such as the Han and native Tibetans, presented with undetectable UA levels. Generally, hypoxia disrupts energy metabolism, accelerating ATP degradation and subsequently enhancing purine metabolite production (Tran-Thi et al. 1994). Hypoxia also stimulates erythropoiesis, increasing the enucleation of mature red blood cells, which further elevates purine metabolism (Anderson et al. 2018; Semenza 2022). These processes ultimately lead to increased synthesis and accumulation of blood UA, peaking around 30 days of hypoxic exposure (Sinha et al. 2009; Bartziokas et al. 2014; Du et al. 2022). Interestingly, we found that 40.53% of fecal metabolites under exposure belong to Cluster 1, the most abundant cluster type that changes significantly at the LS2 time point. This suggests that the critical time point for gut metabolic rewiring under high-altitude exposure likely occurred around 1 month. Nevertheless, UA is not directly utilized by the body and is excreted via the kidneys (2/3 load) and intestines (1/3 load) (Yanai et al. 2021). Under hypoxic conditions, renal clearance is impaired, and elevated blood lactate levels competitively inhibit UA excretion, reducing renal clearance by 70% to 80%, leading to UA accumulation (Vij et al. 2005; Mao et al. 2024). This accumulation is associated with oxidative stress and cardiovascular diseases (Hayden and Tyagi 2004; Hurtado-Arestegui et al. 2018), as well as endothelial dysfunction and mitochondrial damage (Yin et al. 2019; Liu, Xu, et al. 2023; Liu, Jarman, et al. 2023). Additionally, it significantly impacts intestinal health and potentially leads to hyperuricemia and gout (Sahebjami and Scalettar 1971; Vij et al. 2005; Lv et al. 2020, 2021). These findings underscore the significance of intestinal UA clearance in hypoxic environments and suggest an adaptive rewiring of UA metabolism in the intestine, facilitating effective adaptation to high altitudes.

Further investigation disclosed a strong link between UA metabolic rewiring and gut microbiota composition. The gut microbiota regulates intestinal UA levels through various mechanisms, including influencing host metabolic pathways and immune responses, promoting gut health, and facilitating UA excretion. Certain gut bacteria have been reported to enhance UA breakdown, thereby reducing its concentration in the body. For instance, some bacteria can convert UA into nucleotides that support bacterial DNA synthesis (Goncheva et al. 2022) and improve hyperuricemia by inhibiting xanthine oxidase, a key enzyme in UA synthesis (Wang et al. 2019). Additionally, compared to healthy individuals, gout patients exhibit significantly lower levels of microbial metabolism related to butyrate biosynthesis, which can enhance the intestinal immune barrier, reduce inflammation, promote the growth of beneficial microbes, and facilitate UA excretion and clearance (Cleophas et al. 2016; Guo et al. 2016).

Here, we identified a proliferation of UA-degrading bacteria, predominantly from the Lachnospiraceae family, known for their anti-inflammatory properties (Zhang et al. 2019). These bacteria were significantly more abundant during short-term hypoxia exposure and maintained high levels among long-term high-altitude residents. This observation, in combination with previous studies, suggests their potential to degrade UA by (i) consuming UA, (ii) reducing intestinal inflammation and influencing host metabolism through bacterial metabolites like butyrate, ultimately enhancing UA transport and excretion (Wang and Ye 2024), and (iii) compensating for the loss of uricase to maintain UA homeostasis (Wang and Ye 2024). Furthermore, in line with the most significant changes in the gut microbiome at LS2 time point (Su et al. 2024), there is a simultaneous peak in both UA-degrading bacteria and UA levels at LS2, thereby reinforcing the gut microbiota's integral part in the intestinal UA metabolic rewiring.

In conclusion, our study has unveiled a strategic metabolic rewiring of UA in the intestine, representing an essential adaptation strategy that extends beyond a mere response to hypoxia. This rewiring appears to enable the host to regulate UA balance through gut bacteria, offering a foundation for microbiota-focused interventions in managing and preventing altitude-related ailments. Further investigation is needed to verify these relationships and mechanisms.

Materials and Methods

Study Population

From 2019 July 11 to October 26, we recruited 46 healthy male students, aged 21 to 27, with an average body mass index of 22.23 ± 1.97 kg/m^2 (mean $\pm$ SD), for health examination at Lhasa Hospital. These participants were selected based on their lack of cardiopulmonary, metabolic, dyslipidemic, or gastrointestinal conditions. They provided the required information, written informed consent, and biospecimens, including fresh morning fecal samples at seven time points. The study received ethical approval from and the Ethics Committee at Kunming Institute of Zoology, Chinese Academy of Sciences (approval number: KIZRKX-2021-010).

Fecal Sample Collection

Fecal samples were systematically collected from 46 male participants aged 21 to 27 years across seven time points: 10 days prior to departure (CQ1, serving as the control) and at 2 (LS1), 24 (LS2), 45 (LS3), and 66 (LS4) days following arrival in Lhasa. Additional collections were conducted 1 week (80 days; CQ2) and 3 weeks (98 days; CQ3) after their return to lowland (Fig. 1a). None of the participants had been to a high altitude within 6 months before the study began. Participants were required to fast overnight for at least 8 h before sample collection. In total, 260 stool samples were collected from participants in a fasting state in the morning, including 44 at CQ1, 44 at LS1, 43 at LS2, 44 at LS3, 43 at LS4, 20 at CQ2, and 22 at CQ3, corresponding to the seven time points. All samples were immediately preserved at −80 °C. The genomic DNA of all fecal samples (from the seven time points) was extracted at the same time in the lab.

Metabolome Profiling of Fecal Samples

Fecal metabolite extraction was conducted using a 1:1 acetonitrile:methanol solution containing an isotopically labeled internal standard mixture. Analysis was performed on a UHPLC-QTOF-MS/MS system (Vanquish, Thermo Fisher Scientific, Bremen, Germany). The separation of metabolite extracts was achieved using a Waters Amide column (2.1 mm × 100 mm, 1.7 µm). We injected 2 µL of the metabolite solution and performed the elution using a mobile phase composed of phase A (25 mmol/L ammonium acetate and 25 mmol/L ammonium hydroxide in water, pH = 9.75) and phase B (acetonitrile), with a flow rate of 0.5 mL/min. The gradient was as follows: 95% B for 0 to 0.5 min, a linear gradient from 95% to 65% B over 0.5 to 7 min, 65% to 40% B over 7 to 8 min, held at 40% B for 8 to 9 min, a sharp increase from 40% to 95% B over 9 to 9.1 min, and then held at 95% B for 9.1 to 12 min. Metabolic fragments were acquired using a Q Exactive HFX mass spectrometer (Orbitrap MS, Thermo) coupled with electrospray ionization (ESI). ESI source settings were MS/MS resolution at 7,500, capillary temperature at 320 °C, and full MS resolution at 60,000. Ion spray voltage floating was set at 3.5 kV in positive mode and −3.2 kV in negative mode. A total of 7,059 peaks in positive mode and 4,599 peaks in negative mode were detected. Raw data were converted to mzXML format using ProteoWizard (v3.0) and processed with the R package XCMS for peak detection, extraction, alignment, and integration (Want et al. 2006). Metabolite annotations were performed using public databases (METLIN, HMDB, KEGG, CHEBI, mzCloud, mzVault, and LIPID) with a cutoff of 0.3, and duplicates were filtered based on LC-MS/MS scores.

Fecal volatile organic compounds were analyzed using an Agilent 7890 gas chromatograph with a DB-5MS capillary column (30 m × 250 µm × 0.25 µm, J&W Scientific, Folsom, CA, USA). MS-DIAL software (v4.0) was utilized for raw peak extraction, baseline filtering and calibration, peak alignment, deconvolution, identification, and integration of peak areas (Tsugawa et al. 2015). The Fiehn BinBase database was employed for metabolite identification, which included mass spectral and retention time index matching (Kind et al. 2009). After excluding QC samples with peak detection below 0.5 (Dunn et al. 2018), 1,175 fecal metabolite peaks were identified, and 2,612 features were detected in experimental samples. Of these, 2,311 metabolites with a high MS/MS similarity score (>60) were retained for further analysis.

Differential metabolites were identified using the Wilcoxon rank-sum test and adjusted by the FDR method. Criteria for screening included a VIP score of >1.0 and an FDR of <0.2 (Li et al. 2019; Fu et al. 2020). In total, 190 distinct fecal metabolites were identified when comparing baseline to the other six time points (supplementary table S1, Supplementary Material online). Metabolite annotation was conducted using the KEGG database (https://www.genome.jp/kegg/pathway.html), and VIP scores were calculated with MetaboAnalyst (v5.0) (Pang et al. 2021). Pathway enrichment (KEGG level C pathways) was analyzed using MBROLE3 (http://csbg.cnb.csic.es/mbrole3/index.php) (Huang et al. 2012), and metabolism-related functions were further examined. Graphs were generated in R (v4.0.2).

Dynamic Change Analysis (Mfuzz)

Fuzzy c-means clustering, a soft clustering approach, was executed using the R package Mfuzz (v2.54.0) (Kumar and Futschik 2007). We clustered differential fecal metabolites with the "Mufzz" function to delineate dynamic patterns of change. The optimal number of clusters was determined using the "WSS" and "Gap statistic" methods in Mfuzz (supplementary fig. S1, Supplementary Material online).

UA-Inducible Gene Prediction Based on Fecal Metagenomics

The five UA-inducible genes (*ygeX*, *ygeY*, *ygeW*, *ygfK*, and *ssn*A) were predicted from 1,079 high-quality species-level genomes (SGBs) derived from fecal metagenomic data of the same cohort (Su et al. 2024). These genes were chosen for their role in encoding enzymes that utilize UA and contribute to the maintenance of host UA homeostasis (Kasahara et al. 2023; Liu, Xu, et al. 2023; Liu, Jarman, et al. 2023). The conserved protein sequences of these five genes across different species were retrieved from the InterPro database (https://www.ebi.ac.uk/interpro/) (Paysan-Lafosse et al. 2023). Using BITACORA (v1.4.1) (Vizueta et al. 2020), we predicted the distribution of these genes with parameters set to an *E*-value of $1e^{-3}$ and a filter length of 50. Out of 586 SGBs, a total of 94 contigs displayed complete UA metabolic potential (encompassing all five UA-inducible genes). These 94 contigs are considered potential UA gene clusters. For further analysis, 71 contigs (supplementary table S4, Supplementary Material online) met stringent quality criteria: (i) genes classified as outliers, exceeding 1.5 times the interquartile range [q75 to q25], were excluded; and (ii) sequences 10-kb upstream and downstream of the five genes were retained, ensuring the total length did not surpass 50 kb.

The Validation Populations Resided at High Altitude for a Long Time

To further investigate the association between UA consumption by gut microbiota and adaptation to high-altitude hypoxia, we expanded our analysis to include fecal metagenomic and metabolomic data from 163 independent Han Chinese residents of Shigatse, Xizang (a.s.l. 4,700 m), with residency durations ranging from 5 to 60 months. We also incorporated fecal metabolomic data from 28 native Tibetans residing in the same region. The analytical approach for fecal metabolomic and UA gene cluster identification was aligned with the previously described methods. A total of 1,166 high-quality SGBs were selected for UA gene cluster prediction and analysis. However, the abundance of UA and urate in the feces were below the

detection threshold of the Q Exactive HFX mass spectrometer; therefore, the fecal metabolomic results are not reported here.

Statistical Analysis

PLS-DA for the metabolome and microbiome data was conducted using the "*plsda*" function from the R package mixOmics (v6.18.1). Indicator species analysis was used to evaluate the dominant gut microbiota at various stages of high-altitude exposure, considering $P < 0.05$ as statistically significant (Leff et al. 2018). To assess significant differences in analytes between time points, we employed the Wilcoxon rank-sum test (paired). The KEGG pathway enrichment was analyzed using Fisher's exact test, focusing on the ratio of annotated metabolite counts to the total counts within specific pathways.

Supplementary Material

Supplementary material is available at *Molecular Biology and Evolution* online.

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Author Contributions

Q.-P.K. designed and supervised the study, while Y.-C.L., Y.-J.L., Y.C., M.-X.G., X.-Y.L., F.-Q.Y., Y.-M.H., Z.-L.G., Y.-X.Z., Q.Z., and L.Z. were responsible for the sample collection. Z.-L.G., L.Z., and L.-Q.Y. performed total DNA extraction from the samples. Data analysis was carried out by Q.S., D.-H.Z., T.-Y.X., Q.S., and D.-H.Z. contributed to writing the manuscript. Y.-C.L., Q.-P.K., and Z.Z. provided valuable suggestions and made modifications to the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Institute Research Medical Ethics Committee of the Army Medical University, the Ethics Committee at Kunming Institute of Zoology, Chinese Academy of Sciences. A written informed consent was obtained from each participant.

Conflict of Interests

The authors declare that they have no competing interests.

Data Availability

All metagenomic sequencing data generated and analyzed in the present study have been deposited in the Genome Sequence Archive in the National Genomics Data Center (https://bigd.big.ac.cn/gsa/; accession number: subHRA005186).

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