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REVIEW

High-altitude exposure remodels the gut microbiota: health and disease

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Abstract **With the increasing number of individuals travelling to or residing in high-altitude regions, understanding the physiological and pathological consequences of such environments has become increasingly important. High-altitude exposure poses significant challenges to human health, primarily due to hypobaric hypoxia, which triggers a cascade of responses, including energy deficiency, oxidative stress, and inflammation. One of the critical consequences is the disruption of the gut barrier, which facilitates the translocation of the gut microbiota and further exacerbates local and systemic inflammation. Notably, the gut microbiota, a dynamic environmental sensor, undergoes significant remodelling in high-altitude environments. The modified production of microbial metabolites such as bile acids influences gut homeostasis as well as glucose and lipid metabolism, and ultimately contributes to individual variability in high-altitude acclimatization. These changes have been implicated in the pathogenesis of altitude-related illnesses such as acute and chronic mountain sickness, as well as in metabolic and gastrointestinal disorders such as diabetes, obesity, irritable bowel syndrome, colorectal cancer, cholelithiasis, and osteoporosis. Preliminary explorations have demonstrated the therapeutic potential of microbiome-based interventions such as faecal microbiota transplantation in acute and chronic mountain sickness. Further research into gut microbiota modulation may provide applicable options for promoting high-altitude acclimatization and preventing high-altitude illness.**

Keywords gut microbiota; hypoxia; gut barrier; acclimatization; mountain sickness

Introduction

High-altitude environments feature decreased barometric pressure, low oxygen, low air temperature, and strong solar radiation [1,2]. With further economic development and increased tourism, millions of people make short-term journeys to high-altitude regions for work or travel every year [3,4]. As a result of the rapid reduction in oxygen, unacclimatized individuals can suffer from acute mountain sickness (AMS), the incidence of which reaches 50%, and some severe cases even progress to high-altitude pulmonary and cerebral edema [5–7]. Moreover, more than 80 million people live above 2500 m worldwide, accounting for 1.07% of the total population [8]. These individuals are at risk of chronic mountain sickness (CMS), with a prevalence ranging from 4.5% to 44.1%, which varies significantly with altitude [9–11]. The severe risks imposed by high-altitude environments on visitors and residents highlight the essential importance of comprehending high-altitude pathophysiology.

The gut microbiota, a dynamic community consisting of numerous bacteria, fungi, viruses, archaea, and microscopic eukaryotes, is remodelled by this extreme

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environment [12–14]. The gut microbiota participates in physiologic activities such as nutrient digestion and absorption, vitamin synthesis, gut barrier maintenance, and pathogen defense [15,16]. The gut microbiota maintains gut homeostasis through extensive interactions with gut epithelial cells and immunocytes, and communicates with other organs through neural, endocrine, immunological, and metabolic pathways [17–21]. An extensive variety of microbial molecules and metabolites, such as pathogen-associated molecular patterns (PAMPs) (e.g., peptidoglycan, mannan, lipoproteins, and lipopolysaccharide (LPS)) and short-chain fatty acids (SCFAs), are involved [17,18,22]. In this study, we synthesize current evidence on gut microbiota alterations induced by high-altitude exposure (Table 1), discuss potential mechanisms linking the gut microbiota to high-altitude health, and review microbial therapeutic options for high-altitude illness. To ensure research currency, we primarily included peer-reviewed studies published between April 2000 and March 2025 that investigated the gut microbiota in the context of high-altitude exposure, acclimatization, and disease.

Gut microbiota in the physiologic state

Detection approaches and microbial profiles

Among the commensal microbes inhabiting the gastrointestinal tract, bacteria greatly outnumber eukaryotes and archaea, and the abundance of bacteria in the colon greatly exceeds that in the stomach, duodenum, jejunum, and ileum [13,22]. Next-generation sequencing technologies, including 16S rRNA sequencing (for bacteria), 18S rRNA sequencing (for eukaryotes), internal transcribed spacer sequencing (for fungi), shotgun metagenomics, metatranscriptomics, and virome, facilitate comprehensive profiling of the gut microbiota [39]. Given the predominance of bacterial populations in the colon, faecal 16S rRNA sequencing is the primary methodological choice. The gut microbiota exhibits functional redundancy among different bacterial strains, accompanied by intricate metabolic cross-feeding interactions between strains. Shotgun metagenomic sequencing alleviates the biases from primer selection and represents the most effective approach to obtain both structural and functional data. Other techniques such as microbial culture, real-time quantitative polymerase chain reaction, and serum antibody detection have been used to screen specific opportunistic pathogens (e.g., *Clostridium difficile*, Epstein-Barr virus, and cytomegalovirus) [40–42]. Gut fungi and viruses affect host immunity and intestinal homeostasis through extensive interactions with both gut bacteria and the host [43–45]. Gut fungi produce metabolites such as antimicrobial peptides (AMPs) and alcohol to influence the colonization of bacteria, whereas phages (> 90% of the gut viruses) shape the composition of gut bacteria via replication cycles. However, methodological heterogeneity remains a major limitation in microbiome studies [46]. Differences in sequencing depth, target regions, and bioinformatic pipelines can introduce substantial variability, making direct comparison across studies challenging. Standardized analytical frameworks and multi-kingdom integrative approaches are therefore essential for improving data comparability and reproducibility.

Mitochondrial butyrate β-oxidation in terminally differentiated colonocytes, a highly oxygen-consuming process, reduces oxygen diffusion into the intestinal lumen, thereby preserving the predominance of obligate anaerobes in the colonic microbial community [47]. Aerobic and facultative anaerobic bacteria are located mainly in the jejunum and ileum [48]. In healthy adults, dietary changes drive transient shifts in the gut microbiota, but the core bacterial species remain stable. Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, and Verrucomicrobia are the main bacterial phyla, with approximately 90% of the total relative abundance accounted for by Firmicutes and Bacteroidetes [49]. The gut microbial enterotypes, categorized by predominant genera such as *Bacteroides* and *Prevotella*, reflect the metabolic capacity of the gut microbiota, which is strongly linked to long-term dietary patterns. The *Prevotella* enterotype is relevant to vegetarians or high-fiber and carbohydrate-rich diets, whereas the *Bacteroides* enterotype is associated with diets rich in animal fats and proteins [50,51]. In addition, other factors, such as environment, lifestyle, and genetic background, drive changes in the gut microbiota [52–54]. Nevertheless, the boundaries between enterotypes are often blurred, and mixed or transitional enterotypes have been reported in multiple cohorts [55,56]. This suggests that the concept of distinct enterotypes may represent a simplified classification rather than discrete biological entities. Longitudinal and multi-omics analyses will be required to refine our understanding of enterotype stability and its physiologic significance. In general, substantial interindividual variability characterizes the gut microbiota, and the so-called "normal" microbiota represents a dynamic host-commensal balance.

Gut microbiota in intestinal barrier maintenance

AMPs produced by Paneth cells, mucins secreted by goblet cells, intestinal epithelial cells, and cellular junctions are important chemical and physical barriers that defend against pathogens. Immune cells (e.g., dendritic cells (DCs), macrophages, T helper cells, natural killer T cells (NKT cells), and IgA-producing plasma cells) and immune-active substances (e.g., cytokines, antibodies, and lysozyme) in the gut constitute

Table 1 Clinical studies on the gut microbiota at high altitudes

Year	Location	Type	High-altitude exposure	Altitude (m)	Sample size (*n*)	Sample	Sequencing method	Other tests	Reference
2023	China	Longitudinal study	⩽48 hours	>3000	20	Feces	16S rRNA (V3–V4)	Serum and fecal metabonome	Qi *et al*. [23]
2024	China	Longitudinal study	2, 24, 45, and 66 days	3658	45	Feces	Metagenomics	Animal experiment	Su *et al*. [24]
2005	Nepal	Longitudinal study	29 days	5200–6677	7	Feces	Fluorescence *in situ* hybridization	C-reactive protein	Kleessen *et al*. [25]
2020	China	HA vs. LA	4 days, 6 days, >3 months, native	4300	21, 40, 50, 102 vs. 96, 84	Feces	16S rRNA (V3–V4)	Blood clinical indexes	Jia *et al*. [26]
2024	China	HA vs. LA	1 week, >6 months, native	4300	85, 63, 138 vs. 232, 92	Feces	Metagenomics	Plasma metabonome and clinical indices	Han *et al*. [27]
2015	China	HA vs. LA	>4 years, native	3100	12, 12 vs. 11	Feces	16S rRNA (V1–V3)	None	Li *et al*. [28]
2016	China	HA vs. LA	>20 years, native A, native B	3600, 3600, 4800	12, 13, 13 vs. 30	Feces	16S rRNA (V1–V3)	None	Li *et al*. [29]
2020	China	HA vs. LA (Meta-analysis)	Han (Not specified), native	3100–3750	33, 98 vs. 310	Feces	16S rRNA (V3–V4, V4, V4–V5) & Metagenomics	HA vs. LA animal (pig, pika, rex rabbit, rhesus macaque)	Zeng *et al*. [30]
2018	India	HA vs. LA (rural) vs. LA (urban)	Native	3500	35 vs. 25 vs. 24	Feces	16S rRNA (V1–V5)	None	Das *et al*. [31]
2019	Nepal, Bolivia	HA vs. LA	Native	2800–4180	4, 10, 4 vs. 11	Feces	16S rRNA (V3–V4)	Multivariate analysis	Quagliariello *et al*. [32]
2024	China	HA vs. LA	Native	4500	18 vs. 30	Feces	Metagenomics (bacteriome, mycobiome, and virome)	None	Xiao *et al*. [33]
2023	China	HA vs. LA	Not specified	3650–3900	20 vs. 20	Feces	16S rRNA (V3–V4)	HA vs. LA animal (dog, rhesus macaque, coyote)	Zhao *et al*. [34]
2021	China	Immigrants vs. Aborigines	>1 year, native	3900	5 vs. 26	Feces	16S rRNA (V4)	Hematocrit, platelet	Ma *et al*. [35]
2020	China	Immigrants vs. Aborigines	>10 years, native	3658	12 vs. 15	Feces	Metagenomics	None	Li *et al*. [36]
2018	China	Traditional vs. Semi-urban vs. Urban	Native	3100–3660	8 vs. 8 vs. 8	Feces	16S rRNA (V4–V5)	None	Li *et al*. [37]
2017	China	Multivariate analysis (altitude, age, and BMI)	Native	2800–4500	52, 30, 30, 29, 32, 34	Feces	16S rRNA (V4)	None	Lan *et al*. [38]
2022	China	Multivariate analysis (environment, diet, drug, etc.)	Native	3300–5100	586	Feces	16S rRNA (V3–V4)	None	Li *et al*. [14]

Studies are organized according to research type, exposure duration and population characteristics, ranging from acute exposure to prolonged residence and native populations. Substantial heterogeneity exists among studies in altitude definition, exposure duration, sequencing methodology, and sample size, which may limit the direct comparability of results.

Abbreviations: HA, high altitude; LA, low altitude; BMI, body mass index.

the intestinal immune barrier, and gut-associated lymphoid tissues, innate lymphoid cells, and intraepithelial lymphocytes are the core components [16,57–61]. Toll-like receptors (TLRs), the most thoroughly characterized pattern recognition receptors widely expressed in immune cells and intestinal epithelial cells, recognize exogenous PAMPs (e.g., bacterial LPS, peptidoglycan, lipoprotein, flagellin, ssDNA, and CpG DNA) and internal damage-associated molecular patterns to activate the nuclear factor-kappa B (NF-κB) pathway, whereas myeloid differentiation factor 88, the core adaptor of TLRs, initiates both innate and adaptive immune responses [60,62,63]. This inflammatory response is critical for preventing pathogen translocation, while PAMP stimulation further promotes the maturation of the intestinal immune barrier, thereby increasing immune tolerance (Fig. 1).

The gut microbiota ferments dietary fibers and host mucins to produce SCFAs (free fatty acids containing fewer than 6 carbon atoms, mainly acetate, propionate, and butyrate), and Bacteroidetes, *Bacteroides* spp., *Clostridium* spp., *Prevotella* spp., *Bifidobacterium* spp., and *Ruminococcus* spp. are major participants [64–66]. *Faecalibacterium prausnitzii,* formerly known as

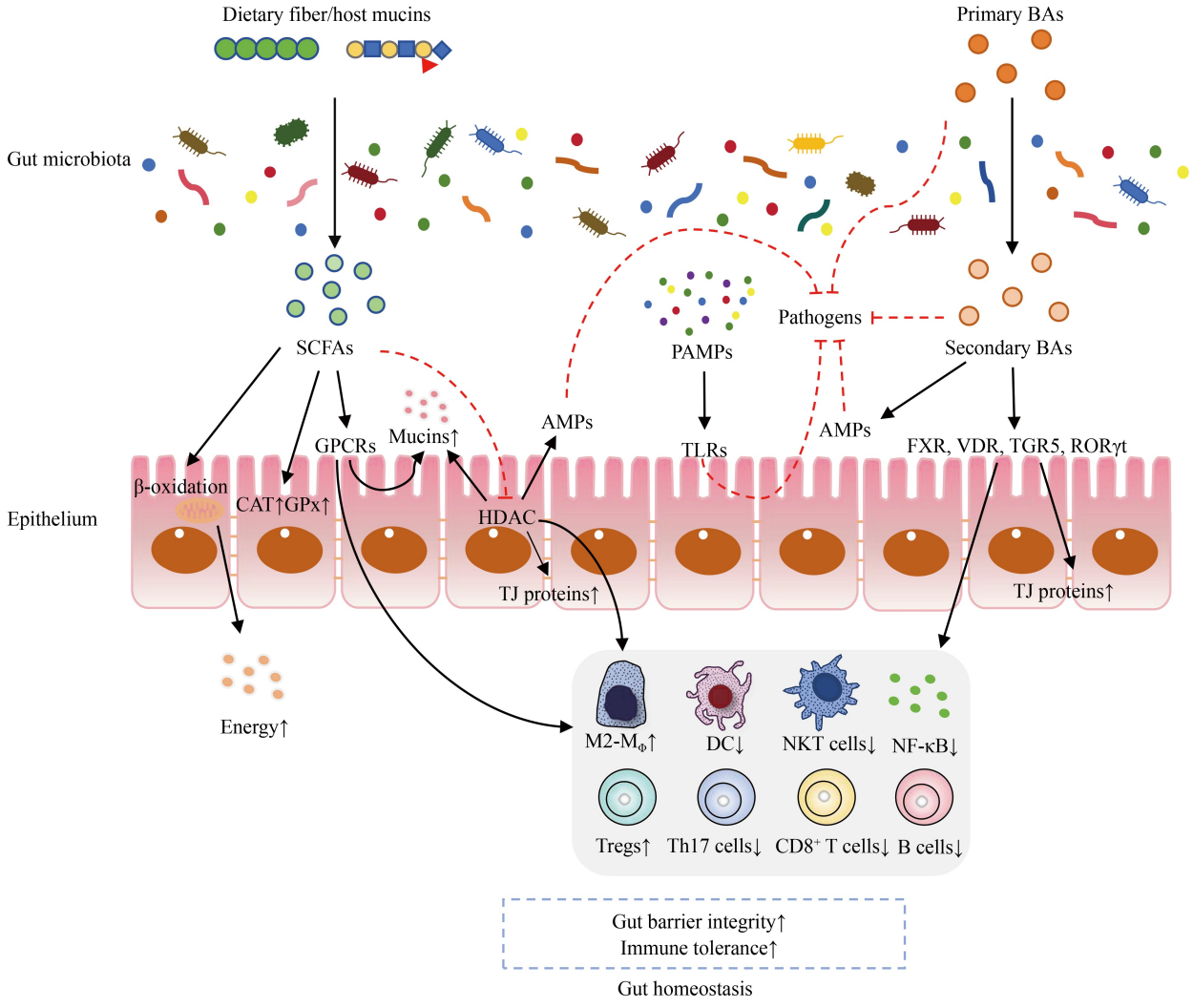

Fig. 1 The gut microbiota maintains gut barrier integrity and immune tolerance. SCFAs act as the primary energy source for colonocytes and activate enzymatic antioxidant defenses, while bile acids exert direct antimicrobial activity. SCFAs and bile acids also inhibit histone deacetylase (HDAC) (mainly butyrate) and activate receptors in immune cells and intestinal epithelial cells to increase the expression of cellular junction proteins, mucins, and AMPs; promote macrophage polarization to the immune-tolerogenic phenotype (M2); promote the differentiation of regulatory T cells (Tregs); inhibit the differentiation and maturation of DCs and T helper 17 cells (Th17 cells); suppress the proliferation of B cells, $CD8^+$ T cells, and NKT cells; and inhibit NF-κB activation and proinflammatory cytokine release to maintain immune tolerance. TLRs recognize exogenous PAMPs and activate the NF-κB pathway to eliminate pathogens. Solid black arrows indicate activation, and dashed red lines indicate inhibition. Abbreviations: CAT, catalase; GPx, glutathione peroxidase; TGR5, Takeda G protein-coupled receptor 5; RORγt, retinoid-related orphan receptor γt; GPCRs, G protein-coupled receptors; VDR, vitamin D receptor; M_Φ, macrophage; FXR, farnesoid X receptor; TJ, tight junction.

Fusobacterium prausnitzii, is the most important butyrate producer and accounts for 20% of the microbiota in the proximal colon [67–69]. *Akkermansia muciniphila*, a specialist in mucin degradation that belongs to Verrucomicrobia, colonizes the colonic outer mucus layer, utilizes mucins as the only carbon and nitrogen source by degrading *O*-glycans to produce acetate and propionate, and promotes the renewal of the inner mucus layer [64,66,70]. SCFAs act as the primary energy source for colonocytes (60%–70%), and very small amounts absorbed into the blood serve as substrates (acetate and propionate) for hepatic gluconeogenesis, cholesterol synthesis, and long-chain fatty acid synthesis. Moreover, as an intermediate product of propionate formation, succinate activates intestinal gluconeogenesis [71,72]. As preferred energy sources, butyrate and acetate directly protect isolated colon cells against reactive oxygen species (ROS)-induced DNA damage [73]. In addition, SCFAs (particularly propionate) activate enzymatic antioxidant defenses in intestinal epithelial cells by increasing the activity of catalase and glutathione peroxidase to mitigate TNF-α-induced lipid peroxidation [74]. SCFAs also inhibit histone deacetylases (mainly butyrate) and activate G protein-coupled receptors in intestinal epithelial cells and immune cells to increase the expression of mucins, AMPs, and tight junction proteins; promote regulatory T cell (Treg) differentiation; and inhibit NF-κB activation and proinflammatory cytokine secretion [64,75–77]. However, inconsistencies exist among studies regarding the magnitude and direction of SCFA-mediated immune effects. Variations in experimental models (*in vitro* vs. *in vivo*, human vs. rodent), SCFA concentrations, and receptor specificity (GPR41 vs. GPR43 vs. GPR109A) contribute to divergent findings concerning Treg induction and anti-inflammatory potential [78–80]. These discrepancies highlight the need for physiologically relevant human studies and standardized metabolite quantification to clarify the immunomodulatory capacity of SCFAs. Taken together, the gut microbiota produces SCFAs for energy supply, antioxidation, and immune regulation (Fig. 1).

Moreover, the gut microbiota (e.g., *Bifidobacterium* spp., *Clostridium leptum*, *Ruminococcus gnavus*, and *Blautia producta*) in the terminal ileum and colon deconjugate conjugated bile acids (approximately 15%) with bile salt hydrolases and transform primary bile acids into secondary derivatives through oxidation, epimerization, and dehydroxylation [81,82]. In addition to facilitating lipid and fat-soluble vitamin absorption, bile acids modulate gut homeostasis. On the one hand, hydrophobic bile acids exert direct antimicrobial activity by altering the lipid composition of the cellular membrane and dissociating integral membrane proteins [81,83,84]. On the other hand, primary and secondary bile acids interact extensively with immune cells and intestinal epithelial cells. For example, chenodeoxycholic acid (CDCA) activates nuclear farnesoid X receptor (FXR) to block myosin light chain kinase activation induced by LPS and promote tight junction protein expression [85]. Lithocholic acid (LCA) promotes the production of the antimicrobial peptide LL-37 by increasing *CAMP* transcription [86] and activates the nuclear vitamin D receptor to upregulate cellular junction protein expression [87]. Furthermore, through binding to the nuclear retinoid-related orphan receptor, FXR, vitamin D receptor, and membrane Takeda G protein-coupled receptor 5 in immune cells, CDCA, LCA, and 3-oxo-LCA promote macrophage M2 polarization; suppress the differentiation and maturation of dendritic cells; inhibit the differentiation of Th17 cells; and suppress the proliferation of B cells, $CD8^+$ T cells, $CD4^+$ T cells, and NKT cells to maintain immune tolerance [82,88,89]. In addition, isoallo-LCA can increase the production of mitochondrial ROS to promote $FoxP3^+$ Treg differentiation [90]. Nevertheless, the specific immunological consequences of bile acid signaling remain debated [91–94]. Some studies emphasize FXR-dependent epithelial protection, whereas others suggest that excessive FXR activation may impair mucosal repair and exacerbate inflammation. Similarly, conflicting results exist regarding the relative importance of FXR versus VDR signaling in regulating intestinal immune tolerance. Integrating targeted metabolomics with cell-type-specific receptor analyses will be critical to resolve these inconsistencies. To summarize, the gut microbiota modulates host homeostasis by altering bile acid profiles (Fig. 1).

Notably, commensal microbiota and other microbial metabolites, such as indole and hydrogen sulfide, also act on intestinal epithelial cells and immune cells through other mechanisms (e.g., the inhibition or promotion of long non-coding RNAs such as ENO1-IT1 and HIF1A-AS2) to modulate gut homeostasis [22,88,95–97]. However, most evidence arises from *in vitro* studies or animal models, and their relevance in human physiology remains incompletely understood. We focused primarily on SCFAs and bile acids because chronic hypobaric hypoxia induces significant alterations in both their profiles in faecal samples [98]. Overall, microbial molecules and metabolites enhance gut barrier integrity and maintain immune tolerance through coordinated actions on both epithelial and immune cells.

Under physiologic conditions, the gut microbiota contributes to intestinal homeostasis through a delicate interplay among microbial metabolites, epithelial integrity, and immune regulation. However, when individuals are exposed to extreme environmental stressors—such as hypobaric hypoxia at high altitudes (inadequate oxygen supply to cells and tissues due to low ambient air pressure)—this equilibrium can be

profoundly disrupted. Environmental challenges, including low oxygen tension, temperature fluctuations, and dietary shifts, reshape microbial community composition and metabolic output. In the following section, we summarize recent findings on how high-altitude exposure remodels the gut microbiota, with an emphasis on temporal fluctuations, adaptive microbial signatures, and the convergence of immigrant microbiota toward native patterns.

High-altitude exposure remodels the gut microbiota

Microbial fluctuation in diversity

According to existing research, the gut microbiota fluctuates greatly in the initial phase of reaching high altitudes and tends to stabilize with longer durations of residence. The Shannon indices increase within the first 48 hours after ascension to high-altitude regions but decline significantly with prolonged residence [23,24,26,27]. Similarly, the relative abundance of facultative anaerobic bacteria increases at the early stage but decreases later [26], which contributes to fluctuations in diversity. In addition, the relative abundance of aerobic bacteria persistently decreases, whereas that of anaerobic bacteria remains stable [26]. This mainly results from the sharp reduction in luminal oxygen due to hypoxia and contributes to the decrease in microbial diversity. Moreover, direct damage by ROS and reactive nitrogen species and direct killing of immune cells, both resulting from oxidative stress and inflammation, also lead to gut microbiota remodelling.

The overgrowth of potential faecal pathogenic bacteria, including gamma subdivisions of *Proteobacteria*, *Escherichia coli*, and *Klebsiella pneumoniae*, increases the serum C-reactive protein level. A positive correlation between the serum C-reactive protein level and these pathogens has been revealed in mountaineers who gradually ascended above 5000 m within 10 days and continued to rise [25]. Epithelial injury due to prolonged hypoxia triggers the excessive proliferation of stem cells into undifferentiated transit-amplifying cells. These dividing cells obtain energy through anaerobic glycolysis, resulting in high glucose consumption, low oxygen utilization, and pronounced lactate efflux, along with elevated levels of both inducible nitric oxide synthase (iNOS) and its enzymatic product, nitric oxide [47,99]. The increased nitrate and oxygen in the intestinal lumen promote the expansion of these facultative anaerobes, such as *E. coli* [100]. Despite general agreement that microbial diversity fluctuates during altitude exposure, substantial discrepancies remain among studies regarding the magnitude and duration of these changes. Some investigations have reported a transient rise in diversity indices followed by a decline, whereas others have shown no significant variation or even a continuous decrease in α-diversity. These inconsistencies likely stem from differences in sequencing platforms, statistical normalization methods, sampling time points, dietary control, and host adaptation status.

Taken together, these findings depict a transient disturbance of gut microbial ecology immediately after ascent, followed by gradual stabilization as hypoxia persists. To better understand the adaptive process underlying this transition, longitudinal studies have been conducted to capture temporal microbial dynamics during acclimatization, as summarized below.

Microbial signatures of acclimatization (longitudinal evidence)

Numerous factors influence the composition of the gut microbiota [52–54], and a well-designed study focusing on the effects of altitude must control for other confounding factors. Disappointingly, only two small-sample studies have taken this into consideration [23,24]. In addition, contradictory results concerning microbial changes within 48 hours were reported in these studies, which might result from factors such as different destinations (Gannan vs. Lhasa), sequencing methods (16S rRNA vs. shotgun metagenomics), and small sample sizes (20 vs. 45). Therefore, we must adopt current findings with caution. Moreover, these inconsistencies highlight the difficulty of disentangling altitude-specific effects from confounding variables such as travel stress, dietary adaptation, and baseline microbiota composition. The absence of uniform altitude thresholds and inconsistent reporting of ascent rates further complicate inter-study comparisons. Individuals who ascend to high-altitude regions with discomfort usually adapt within 2 or 3 days [101–103]. The increase in *Bacteroides*, *Faecalibacterium*, *Alistipes*, *Odoribacter*, *Parabacteroides*, and *Akkermansia* within 48 hours characterizes the initial phase of microbial community assembly [23]. A longitudinal time-series study [24] identified *Blautia A* as an indicative microbial taxon relevant to high-altitude acclimatization, and its relative abundance was the highest on Day 24. Other species-level genome bins belonging to Lachnospiraceae also increased significantly throughout the 66-day exposure, and the shifts in Shannon indices also identified Day 24 as a turning point (Table 2). These variations highlight the crucial role of Lachnospiraceae (particularly *Blautia A*) in high-altitude acclimatization and the key time points for the remodelling of the gut microbiota. Nevertheless, the limited temporal resolution makes it difficult to determine whether these microbial shifts reflect true adaptation or transient stress responses. Integrating host physiologic data (e.g., cortisol, oxygen saturation) will be essential to

Table 2 High-altitude exposure and the gut microbiota remodeling

Type	Exposure duration	Diversity	Phylum	Family and genus	Species	Reference
Longitudinal study	⩽48 hours	Shannon ↑	Firmicutes↓, Bacteroidetes↑, Actinobacteria↓, Proteobacteria↓	Relative abundance: *Faecalibacterium*↑, *Bifidobacterium*↓, *Escherichia*/*Shigella* ↓, *Alistipes*↑, etc. Lefse: *Bacteroides*↑, *Akkermansia*↑, *Alistipes*↑, *Enterobacter*↓, etc.	Not specified	Qi *et al*. [23]
Longitudinal study	2 days	Shannon→	Firmicutes↑, Bacteroidetes↓, Actinobacteria↑, Proteobacteria↓	*Blautia A*↑	*Blautia* A↑, *Eggerthella lenta*↑, *Anaerobutyricum hallii*↑, *Streptococcus salivarius*↑, etc.	Su *et al*. [24]
	24 days	Shannon↓	Firmicutes↑, Bacteroidetes↓, Actinobacteria↑, Proteobacteria↓			
	45 days	Shannon→	Firmicutes A↑			
	66 days	Shannon→	Firmicutes A↑, Bacteroidetes↓, Proteobacteria↓			
HA vs. LA	4 days	Shannon→	Firmicutes↓, Bacteroidetes↑, Actinobacteria↓, Proteobacteria↑	*Megamonas*↑, *Lactobacillus*↓	Not specified	Jia *et al*. [26]
	6 days	Shannon↓	Firmicutes↑, Actinobacteria↓, Proteobacteria↓	*Faecalibacterium*↑, *Bifidobacterium*↓, *Megamonas*↓, *Lactobacillus*↓, etc.		
	Immigrant (>3 months)	Shannon↓	Bacteroidetes↑, Actinobacteria↓, Proteobacteria↓	*Faecalibacterium*↑, *Bacteroides*↑, *Bifidobacterium*↓, *Lactobacillus*↓, etc.		
	Native	Shannon→	Firmicutes↓, Bacteroidetes↑, Actinobacteria↓, Proteobacteria↓	*Faecalibacterium*↓, *Bacteroides*↓, *Blautia*↓, *Bifidobacterium*↓, *Lactobacillus*↓, etc.		
HA vs. LA	1 week	Shannon→	Proteobacteria↓	*Escherichia*↓	*Ruthenibacterium lactatiformans*↑, *Hungatella hathewayi*↑, *Clostridium leptum*↑, *Escherichia coli*↓, etc.	Han *et al*. [27]
	Immigrant (>6 months)	Shannon↓	Firmicutes↓, Bacteroidetes↑, Actinobacteria↓, Proteobacteria↓	*Prevotella*↑, *Bacteroides*↑, *Faecalibacterium*↓, *Streptococcus*↓, *Escherichia*↓	81 species ↑ (*Butyrivibrio crossotus*, *Bacteroides* spp., *Prevotella* spp., etc.) 95 species↓ (*Faecalibacterium prausnitzii*, *Blautia wexlerae*, *Bifidobacterium adolescentis*, *Escherichia coli*, etc.)	

(*Continued*)

Type	Exposure duration	Diversity	Phylum	Family and genus	Species	Reference
HA vs. LA	Native	Shannon↑	Firmicutes↓, Bacteroidetes↑, Actinobacteria↓, Proteobacteria↓, Verrucomicrobia↓	*Prevotella*↑, *Faecalibacterium*↓, *Clostridium*↓, *Streptococcus*↓, *Megamonas*↓, *Escherichia*↓	111 species↑ (*Butyrivibrio crossotus*, *Prevotella* spp., *Bacteroides* spp., etc.) 75 species↓ (*Faecalibacterium prausnitzii*, *Blautia wexlerae*, *Bifidobacterium adolescentis*, *Escherichia coli*, etc.)	
	Immigrant (Not specified)	Shannon↓	Bacteroidetes↓, Proteobacteria↑	Enterobacteriaceae↑, Ruminococcaceae↑, *Bacteroides*↓, Lachnospiraceae↓, *Blautia*↓, *Prevotella*↓	Not specified	Zeng *et al*. [30]
	Native			Enterobacteriaceae↑, Ruminococcaceae↑, Lachnospiraceae↓, *Blautia*↓, *Bacteroides*↓	Not specified	
HA vs. LA (rural)	Native	Simpson↓	Bacteroidetes↑, Proteobacteria↓	*Prevotella*↑, *Blautia*↓, *Bacteroides*↓, etc.	unidentified_*Faecalibacterium*↑, unidentified_Lachnospiraceae↑, *Prevotella copri*↑, etc.	Das *et al*. [31]
HA vs. LA (urban)				*Prevotella*↑, *Lactobacillus*↓, *Bacteroides*↓, etc.		
HA vs. LA	Not specified	ACE↑	Firmicutes↓, Bacteroidetes↑, Actinobacteria↓, Proteobacteria↓	*Prevotella*↑, *Akkermansia*↑, *Faecalibacterium*↓, *Bacteroides*↓, etc.	Not specified	Zhao *et al*. [34]
Multivariate analysis	Native	Chao↑ Shannon↑	Bacteroidetes (60.00%), Firmicutes (29.04%), Proteobacteria (5.40%), Actinobacteria (3.85%)	Positive (*Faecalibacterium*, *Bacteroides*, and *Bifidobacterium*) Negative (*Prevotella*, Ruminococcaceae, and Lachnospiraceae)	Not specified	Lan *et al*. [38]
Multivariate analysis	Native	Chao↓	Bacteroidetes and Firmicutes	Positive (*Desulfovibrio*, *Clostridium*, *Akkermansia*, *Succinivibrio*, *Butyrivibrio*, etc.) Negative (*Bacteroides*, *Megamonas*, *Blautia*, *Lachnospira*, etc.)	Not specified	Li *et al*. [14]

Only studies with ⩾20 samples per group were included, and substantial heterogeneity exists among studies. Future investigations employing standardized protocols and integrated multi-omics approaches are warranted to validate altitude-related microbial alterations and elucidate their clinical and physiologic significance.

Abbreviations: HA, high altitude; LA, low altitude; ACE, abundance-based coverage estimator; ↑, increased; ↓, decreased; →, similar.

confirm the functional relevance of these changes. In addition, 12-month moderate-altitude exposure (average altitude = 2900 m) was correlated with a significant increase in *Bacteroidetes*, including *Bacteroides nordii* (*B. nordii*), *B. eggerthii*, *B. cellulosilyticus*, *B. dorei*, *B. ovatus*, *B. thetaiotaomicron*, *B. uniformis*, *Prevotella copri* (*P. copri*), *Parabacteroides distasonis*, and *Parabacteroides merdae*, and a decrease in *Proteobacteria* (e.g., *E. coli*) [104]. However, differences in altitude level, duration of exposure, and analytical normalization may partly explain the inconsistent direction of phylum-level changes reported across cohorts. While some studies observe enrichment of Bacteroidetes, others describe a relative increase in Firmicutes or Actinobacteria under similar conditions, underscoring the need for harmonized study designs and metadata reporting. These longitudinal changes highlight the dynamic microbial landscape during high-altitude acclimatization.

Collectively, these time-resolved observations indicate that the gut microbiota undergoes a stepwise adaptation process—from early instability to progressive reorganization—eventually establishing a new ecological equilibrium. The following section further extends this concept by comparing long-term immigrants with native high-altitude residents to explore whether prolonged residence promotes convergence toward indigenous microbial profiles.

Prolonged residence promotes convergence toward native patterns

According to current evidence, the gut microbiota of high-altitude immigrants gradually approaches native patterns over time. At the phylum level, the abundance of Firmicutes increased throughout the 66-day exposure period in one study, whereas that of Bacteroidetes decreased [24]. However, other studies showed that after 3 and 6 months of residence, the abundance of Firmicutes decreased, whereas that of Bacteroidetes increased, together with a lower Firmicutes-to-Bacteroidetes ratio, which approached the levels observed in high-altitude aborigines [26,27,34]. Similar results have also been reported in immigrants with longer residences (12 months and 5 years) and in native animals such as dogs and wild macaques [34,104]. These discrepancies indicate that microbial convergence is not uniform and may depend on altitude level, diet, and host background. Harmonized study designs and standardized definitions of "long-term residence" are needed to validate this pattern. At the genus level, the abundance of *Faecalibacterium* (particularly *Faecalibacterium prausnitzii*) increased within 3 months but decreased with increasing duration, approaching the relatively lower level in aborigines [23,24,26,27]. Similarly, the relative abundance of *Prevotella* significantly increased after 6 months, approaching the relatively higher level in aborigines [24,27,34]. The timing and extent of these changes vary among studies, likely reflecting differences in dietary fiber intake and microbiota baseline. Controlled dietary studies are required to clarify the contribution of diet versus hypoxia. At the species level, the relative abundances of 14 species significantly changed after residing in high-altitude regions for 1 week [27]. However, after a longer residence time, the number of differential species increased. A total of 81 increased species and 95 decreased species were identified after 6 months of residence, and immigrants and aborigines shared 51 increased species and 57 decreased species [27]. *Prevotella* spp. (e.g., *P. copri*), *Bacteroides* spp. (e.g., *B. thetaiotaomicron*, *B. cellulosilyticus*, and *B. ovatus*), and *Parabacteroides* spp. (e.g., *Parabacteroides distasonis*) increased, whereas *Faecalibacterium prausnitzii* decreased [27,104]. The most abundant species shifted from *Faecalibacterium prausnitzii* in lowlanders to *P. copri* in high-altitude aborigines [27]. Although these findings suggest partial convergence toward native microbiota, most evidence is correlative. Functional validation using metagenomics or metabolomics is needed to determine whether these shifts represent true ecological adaptation or dietary assimilation. In summary, prolonged high-altitude residence is correlated with a reduced Firmicutes-to-Bacteroidetes ratio, an increase in *Prevotella* spp. and *Bacteroides* spp., and a decrease in *Faecalibacterium* in the gut microbiota (Table 2).

Both high-altitude immigrants and aborigines maintain significantly lower Shannon indices than lowlanders do in some studies [30], whereas in other studies, the diversity in high-altitude aborigines is similar to that in lowlanders or even higher [26,27]. Such discrepancies in microbial diversity patterns suggest that acclimatization and long-term adaptation may involve distinct ecological equilibria rather than a single convergent endpoint. Variations in sequencing techniques, sample preservation, and population genetics likely contribute to this heterogeneity. Therefore, interpretations of diversity changes should be made cautiously. The relative abundance of *Bacteroides* increased after 3 months of residence and continued to increase by 6 months, whereas no significant difference was detected between lowlanders and high-altitude aborigines [26,27]. The dominant genera in immigrants (6 months and 1 year of residence) and in aborigines are *Bacteroides* and *Prevotella*, respectively [27,31,35,37,38]. Aborigines on the Tibetan Plateau live a preindustrial lifestyle and have a high intake of highland barley (roasted flour and semidried noodles), sweet tea, potato, yak beef, and buttered tea [37,105], whereas immigrants tend to embrace Westernized diets and lifestyles due to economic development [106]. The

Prevotella enterotype in high-altitude aborigines reflects their high-fiber dietary pattern, whereas the *Bacteroides* dominance in high-altitude immigrants reflects their transition to Westernized dietary patterns. Hence, microbial convergence may partly reflect dietary assimilation rather than genetic or environmental adaptation.

The egl-9 family hypoxia inducible factor 1 (*EGLN1*), peroxisome proliferator-activated receptor alpha (*PPARA*), and endothelial PAS domain protein 1 (*EPAS1*) are well-known adaptation genes for highland aborigines [107,108]. *EPAS1* and *EGLN1* are involved in hypoxia inducible factor (HIF) pathways and encode HIF-2α and prolyl 4-hydroxylase 2, respectively, whereas the *PPARA* gene encodes the protein PPARα to modulate fatty acid oxidation in the liver, heart, and muscle [109–112]. Emerging evidence suggests that gut microbiota-derived metabolites, especially SCFAs like butyrate and propionate, can influence PPAR signaling activation in peripheral tissues, including PPARα and PPARγ pathways [113,114]. For instance, in adipose tissue, butyrate has been shown to activate PPARγ and downstream regulatory circuits in immune/metabolic context [115] and gut microbial metabolites are considered a bridge in the PPAR-microbiota-metabolic organ network [116]. Moreover, a broader review of host-microbiota crosstalk highlights how PPAR family members (including PPARγ) respond to microbial signals in health and disease [117]. We thus propose that in high-altitude populations, altitude-adapted gut microbiota might enhance PPARα activation via metabolite-mediated signaling, thereby optimizing lipid oxidation under hypoxia. These mutations inhibit erythropoiesis and the pulmonary vasoconstriction response and modulate cellular energy metabolism. In addition, high-altitude aborigines such as Tibetans possess evolutionary selection of inflammatory genes, including *TNF*, *IL1A*, *IL1B*, *IL6*, *NOS1*, *NOS2*, *PPARA*, and *TGFBR3* [118]. These genetic selections potentially blunt or sensitize the immune response. Owing to the extensive interactions among the gut microbiota, immune cells, and intestinal epithelial cells, genetic selection exerts pressure on gut microbial ecosystems. However, current studies rarely integrate host genomic and microbiome datasets, leaving the extent to which host genetics directly shape microbial convergence largely unresolved. Multi-omics approaches incorporating host transcriptomics and metabolomics will be essential to establish causal relationships between genetic adaptation and microbial configuration.

In addition, small-sample exploration revealed significantly greater Shannon and Simpson indices of the gut mycobiome and virome in native Tibetans than in lowlanders [33]. At the genus level, *Trichosporon* increased significantly, whereas *Mucor* decreased. There were 1398 differential viral operational taxonomic units (vOTUs) between native Tibetans (1138 vOTUs enriched) and lowlanders (260 vOTUs enriched), and 819 strong correlations between bacterial species and vOTUs. Although these findings suggest that fungal and viral communities co-evolve with bacterial taxa under chronic hypoxia, current evidence remains preliminary. The limited cohort sizes and lack of functional annotation constrain interpretation, and future research integrating multi-kingdom analyses will be necessary to clarify their roles in altitude adaptation.

In summary, the cumulative evidence from Sections 3.1–3.3 indicates that high-altitude exposure induces a multi-phase remodeling of the gut microbiota—from early fluctuations to adaptive stabilization and eventual convergence toward native microbial configurations. These compositional and functional shifts may not occur in isolation but rather accompany systemic physiologic challenges such as hypoxia-induced metabolic reprogramming, oxidative stress, and inflammation. The following section therefore examines how high-altitude environments impose physiologic stress on the host and how these host responses interact with microbial alterations to shape overall adaptation and health outcomes.

High-altitude exposure and physiologic challenges

Hypoxia drives energy deficiency, oxidative stress, and inflammation

Because a sufficient oxygen supply is essential for the tricarboxylic acid cycle and oxidative phosphorylation, hypoxia results in energy deficiency and the accumulation of ROS [119]. Excessive ROS triggers oxidative stress, leading to the impairment of both mitochondrial and extramitochondrial macromolecules, the activation of inflammatory pathways, and the induction of cell death [120,121]. Hypoxia inhibits the activity of prolyl hydroxylases for HIF-α ubiquitination and degradation, and stabilized HIF-α binds to HIF-1β to activate target genes involved in energy metabolism and oxygen transportation [122]. NF-κB, the main proinflammatory transcription factor, shares extensive activators (e.g., tumor necrosis factor-α (TNF-α), ROS, and LPS), regulators (e.g., prolyl hydroxylases), and targets with HIF in inflammation and hypoxia [118,123,124]. Under hypoxic conditions, the crosstalk between the HIF and NF-κB pathways provokes inflammation. In addition, the suppression of mitochondrial functions due to the activation of HIF pathways reversely reduces ROS formation and limits damage [125]. The plasma lactic acid level in individuals after 7 days of high-altitude exposure was significantly greater than that in lowlanders. Despite significant decreases in plasma lactic

acid levels in Han immigrants with 6-month residences and in native Tibetans, their levels remained higher than those in lowlanders [27]. Lactate accumulation from enhanced glycolysis inhibits immunity by driving Treg differentiation and inducing anti-inflammatory M2 polarization of macrophages [126,127]. The levels of serum proinflammatory mediators, such as matrix metalloproteinase-2, interferon-gamma (IFN-γ), macrophage inflammatory protein-1β, and the anti-inflammatory cytokine interleukin-10 (IL-10), are significantly increased [27,128,129], verifying the activation of systemic inflammation at the early stage. Moreover, plasma proinflammatory IL-6 levels are significantly increased in high-altitude immigrants (6 months) and aborigines [27], implying the persistence of low-grade systemic inflammation due to chronic hypoxia. In addition, chronic hypoxia disrupts the phenotype of Tregs, promotes the emergence of exTreg-Th17 cells [130], and weakens the anti-inflammatory effects of Tregs [131,132]. In total, hypoxia leads to energy deficiency, oxidative stress, and inflammation, whereas the activation of HIF pathways limits damage. Although it varies in severity, systemic inflammation persists during high-altitude exposure. However, most evidence is derived from cross-sectional or short-term studies, and interindividual variability in inflammatory and metabolic responses remains poorly characterized. The balance between protective HIF activation and harmful chronic inflammation may differ across populations and exposure durations. Future longitudinal and mechanistic studies are required to clarify these context-dependent outcomes.

Gut barrier impairment and systemic inflammation

Small intestine morphological parameters, including mucosal wall thickness, crypt depth, villous height and villous surface area, were significantly decreased in rats due to acute high-altitude exposure (3 days). Together with the increased expression of iNOS and HIF-1α in the intestinal mucosa, these changes were more obvious at 4767 m than at 3842 m [133]. In addition to the activation of HIF pathways, stabilized HIF-1α in the gut epithelium directly increases the expression of mucins, AMPs, and tight junction proteins to protect gut barrier integrity and defend against pathogens [134]. iNOS is mainly induced by proinflammatory cytokines and microbial PAMPs and catalyzes the synthesis of nitric oxide from oxygen and L-arginine [135]. Macrophages and other myeloid cells (e.g., dendritic cells, neutrophils, and eosinophils) exert antimicrobial effects through the direct and indirect effects of reactive nitrogen species, such as nitric oxide, *S*-nitrosothiols, and peroxynitrite [136]. B cells and $CD14^+TLR4^+$ peripheral blood mononuclear cells (PBMCs) were significantly increased in individuals exposed to 3800 m for 3 days [137]. $CD14^+TLR4^+$ PBMCs recognize LPS and increase the expression of molecules such as macrophage inflammatory protein-1α and IL-6 to defend against gram-negative pathogens (e.g., *Klebsiella pneumoniae* and *E. coli*) [138,139]. The increase in $CD14^+TLR4^+$ PBMCs suggests the involvement of the gut microbiota in inflammatory activation, which results mainly from leakage into the gut. The impairment of the ability of chemical and physical barriers to defend against pathogens in the gut allows the translocation of the gut microbiota [16,140]. The intestinal immune cells recognize microbial PAMPs and activate the NF-κB pathway to eliminate pathogens; however, insufficient clearance results in local and systemic inflammation. Similarly, small intestine impairments, such as edema, gas accumulation, increased histological injury scores, proinflammatory cytokine accumulation (e.g., IL-6), and a reduction in tight junction proteins, have also been revealed in mice exposed to hypoxia for 28–30 days [24,141]. Moreover, compared with lowlanders, healthy high-altitude aborigines exhibit morphological and functional changes in the sigmoid colon mucosa, including reduced and irregular intestinal villi, destroyed glandular epithelium, increased ROS activity, and decreased immunological abilities [142]. Therefore, chronic hypoxia also results in persistent gut barrier impairment, and microbiota translocation via the leaky gut leads to low-grade systemic inflammation. However, most current findings are derived from animal or small cohort studies, and the extent to which these structural changes occur in humans during long-term high-altitude adaptation remains unclear. Standardized imaging and biomarker-based assessments will be necessary to confirm barrier dysfunction and its link to systemic inflammation in larger populations.

Gut microbiota in high-altitude health and disease

Microbial and metabolic adaptation during high-altitude exposure

High-altitude acclimatization refers to the physiologic adjustment of organisms to extreme environments (e.g., in travelers and immigrants), whereas adaptation involves genetic or epigenetic changes after prolonged exposure (e.g., in aborigines) [119]. Hypoxia is the central physiologic challenge during high-altitude exposure and causes energy deficiency, oxidative stress, and systemic inflammation. Recent studies suggest that the gut microbiota acts as a crucial intermediary linking hypoxia-induced metabolic reprogramming with systemic physiologic responses during acclimatization and adaptation.

During the early stage of high-altitude exposure, the gut microbiota exhibits remarkable metabolic plasticity to buffer the effects of acute hypoxia. *Faecalibacterium*, *Bacteroides*, *Alistipes*, *Parabacteroides*, *Akkermansia*, and Lachnospiraceae (particularly *Blautia A*) enriched within 3 months are main SCFA producers [64,143–146]. Lachnospiraceae strains, the microbial signature for high-altitude acclimatization, are mainly butyrate producers [145], whereas *Blautia* strains mainly produce acetate, lactate, and succinate and promote the production of butyrate and propionate by crossfeeding with other bacteria, such as *Faecalibacterium prausnitzii* [69,147,148]. In addition, oxygen deprivation rapidly alters hepatic bile acid synthesis, leading to increased CDCA levels in serum and faeces within 48 h [76,113–115]. The gut microbiota converts CDCA into LCA and its derivatives (e.g., 3-oxo-LCA) [81,82]. Although CDCA and its derivatives can improve gut barrier integrity and promote immune tolerance, excessive accumulation may induce oxidative stress and activate the NLRP3 inflammasome, resulting in IL-1β secretion and mucosal inflammation [149,150]. Conversely, glycochenodeoxycholic acid, glycoursodeoxycholic acid, and glycodeoxycholic acid in the plasma significantly decreased after 1 week [27], which mainly results from suppressed liver synthesis and intestinal reabsorption due to energy deficiency [151,152]. The increase in *Clostridium* spp. (e.g., *Clostridium leptum*) and *Ruminococcus gnavus* within 1 week stabilizes secondary bile acid production [79], reflecting an adaptive microbial compensation mechanism that helps maintain immune and metabolic balance under hypoxia. These findings indicate that microbial metabolism plays a dual role—either protecting or exacerbating intestinal injury—depending on the balance between SCFA production and bile acid transformation (Fig. 2).

With sustained high-altitude residence, the gut microbiota gradually reorganizes into a hypoxia-tolerant ecosystem characterized by reduced butyrate synthesis and increased propionate production. In individuals living for 6 months or longer, the abundance of butyrate-producing taxa such as *Faecalibacterium prausnitzii*, *Subdoligranulum variabile*, and *Butyricicoccus pullicecorum* is decreased [62,79]. Moreover, *Bifidobacterium* produces acetate and lactate at a ratio of 3:2 and promotes the production of butyrate and propionate via crossfeeding [153,154]. The decrease in *Bifidobacterium* spp. also intensifies the reduction in butyrate. As butyrate activates PPARγ in mature colonocytes, which drives mitochondrial β-oxidation to provide energy with high oxygen consumption [100], reduced butyrate production leads to metabolic remodeling toward oxygen-sparing pathways. This adaptation alleviates systemic oxygen shortage [122] but simultaneously fosters a low-grade proinflammatory milieu. Since *Clostridium leptum*, *Ruminococcus gnavus*, *Bifidobacterium* spp., and *E. coli* participate in bile acid metabolism, the decrease in these bacteria disturbs enterohepatic circulation, leading to a decreased bile acid pool and potential barrier dysfunction. Together, these microbial shifts—reduced butyrate synthesis and altered bile acid homeostasis—represent key features of long-term microbial adaptation that balance energy conservation with controlled inflammation (Fig. 2).

In parallel, Bacteroidetes and *Prevotella* expansion supports enhanced acetate, propionate, and succinate synthesis, improving host energy flexibility. Acetate serves as a precursor for cholesterol and fatty acid biosynthesis, while propionate fuels gluconeogenesis in the liver [155]. The *Prevotella*-dominated microbiota produces 2–3 times more propionate than *Bacteroides*-dominated communities, indicating distinct energy strategies across populations. At the host level, this microbial reorganization aligns with the selection of high-altitude adaptation genes such as *PPARA*, *EPAS1*, and *EGLN1*, which jointly optimize energy metabolism and oxygen utilization [124–126]. In Tibetans and Sherpas, *PPARA* variants decrease fatty acid oxidation capacity and promote glucose-based metabolism, a pattern further reinforced by microbiota-derived propionate that ensures sufficient glucose for the brain and erythrocytes under hypoxia [124–126]. Moreover, acetate and propionate act on free fatty acid receptors on enteroendocrine and adipose cells to stimulate peptide YY, leptin, and GLP-1 secretion, thereby delaying gastric emptying and regulating appetite and glucose metabolism. These mechanisms may explain epidemiological findings of a lower prevalence of diabetes and metabolic syndrome among highlanders despite similar or higher rates of abdominal obesity [127–131]. A lower Firmicutes-to-Bacteroidetes ratio and a high *Prevotella*-to-*Bacteroides* ratio have been associated with a lower BMI and greater metabolic efficiency [130–135], consistent with patterns observed in high-altitude residents.

In summary, microbial and host adaptations to high altitude form a coordinated continuum: early microbial metabolic flexibility supports short-term acclimatization, while long-term compositional and functional reorganization underlies sustained physiologic adaptation. This dynamic host-microbiota co-regulation establishes the foundation for understanding altitude-related health and disease.

AMS

Headache, dizziness, fatigue or weakness, and gastrointestinal symptoms are the main symptoms of AMS [119]. Energy crisis, oxidative stress, and inflammation are central to its pathogenesis, resulting in

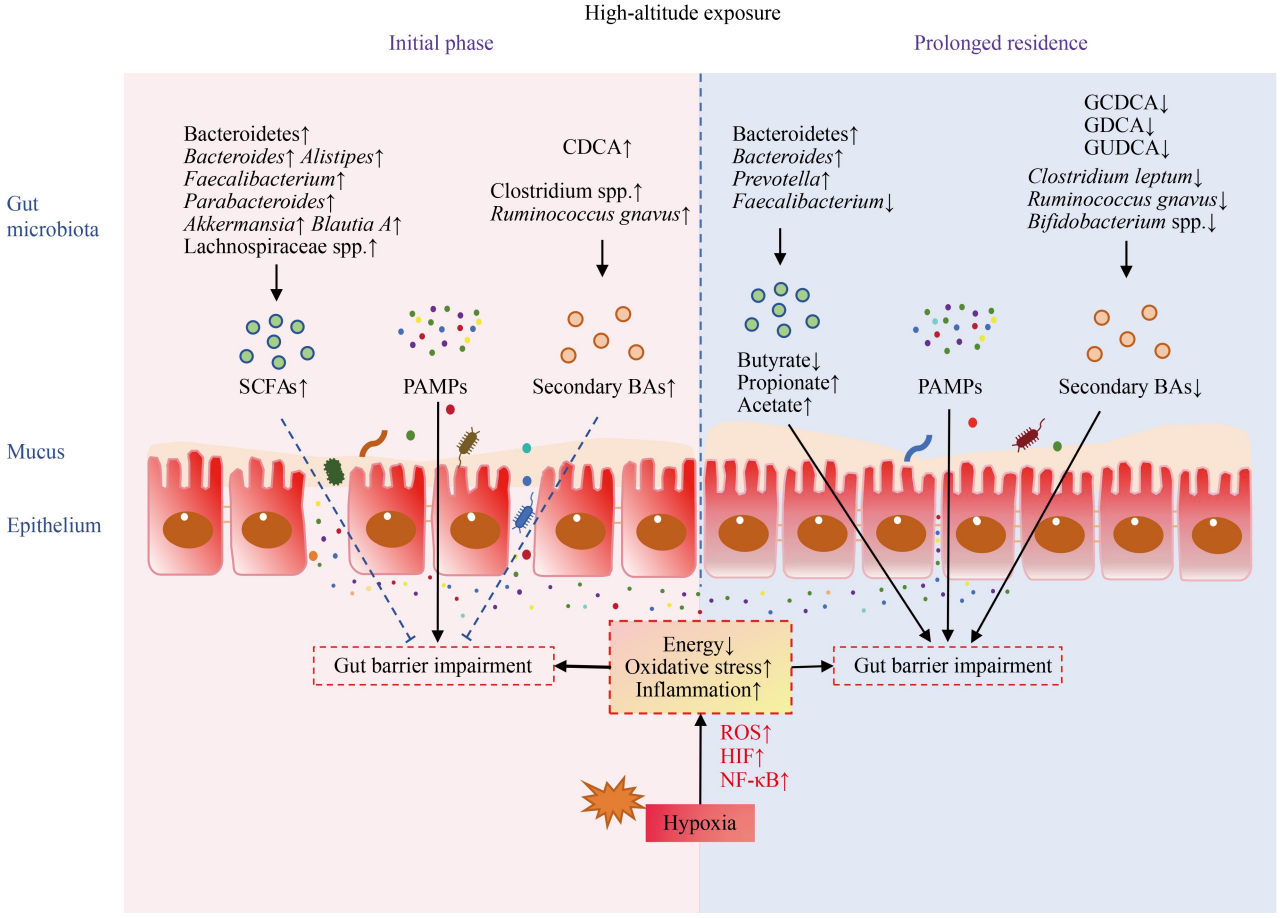

Fig. 2 The multifaceted role of the gut microbiota in intestinal homeostasis during high-altitude exposure. Hypoxia impairs the gut barrier through energy deficiency, oxidative stress, and inflammatory activation, which is more severe in the initial phase and exacerbated by gut microbiota translocation and PAMP stimulation. In the initial phase, the gut microbiota enhances SCFA and secondary bile acid production to restore the gut barrier. However, prolonged residence reduces butyrate production and disturbs bile acid metabolism, thereby aggravating gut barrier impairment. Solid black arrows indicate promotion, while dashed blue lines indicate inhibition. Abbreviations: HIF, hypoxia inducible factor; CDCA, chenodeoxycholic acid; GUDCA, glycoursodeoxycholic acid; ROS, reactive oxygen species; GDCA, glycodeoxycholic acid; GCDCA, glycochenodeoxycholic acid; NF-κB, nuclear factor-kappa B.

gastrointestinal dysfunction and systemic injury (e.g., to the lungs, brain, and heart) [156,157]. Abdominal distension, hyperactive borborygmus, constipation and diarrhea are the most common gastrointestinal symptoms, and 54% (37/69) of cases last for more than seven days [158]. Some healthy trekkers have even developed perforated peritonitis in the Everest trekking region [159]. Staying above 2000 m within 4 weeks has been a risk factor for the flare-up of inflammatory bowel disease (13/52 vs. 4/51, $P = 0.019$) [160], and animal experiments have shown that hypoxia upregulates Th1 and Th17 lymphocytes and exacerbates the colitis induced by dextran sulfate sodium [161]. Acute hypoxia impairs the gut barrier and increases intestinal permeability, leading to microbial translocation and persistent PAMP exposure, which exacerbates local and systemic inflammation and increases the risk of high-altitude cerebral edema (HACE) and pulmonary edema [119]. Appetite suppression and a preference for carbohydrates rather than fats are obvious at the early stage [162,163], and carbohydrates are more efficient in energy production than fat and protein because of their lower oxygen consumption [164]. In one study, individuals who consumed hypocaloric diets during high-altitude exposure were at high risk of moderate or severe AMS (64.7%, 11/17), and a lower *Bacteroides*-to-*Prevotella* ratio and a higher relative abundance of *Prevotella* before ascent were risk factors [165]. This might result from the availability of substrates and the distinct fiber-utilizing and SCFA-producing capacities of *Prevotella* and *Bacteroides*. Owing to the stress response, individuals with moderate or severe AMS presented significantly greater gut microbial Shannon diversity and observed OTUs than those with no or mild AMS did at the second week. The relative abundances of UnclPeptostreptococcaceae, UnclXanthomonadaceae, UnclClostridiaceae, SMB53, *Actinomyces* and

Ochrobactrum were significantly decreased in individuals with moderate or severe AMS, whereas those of UnclClostridiaceae, *Ochrobactrum* and SMB53 were significantly increased in individuals with no or mild AMS [165]. Because Clostridiaceae are involved in intestinal bile acid biotransformation, whereas Peptostreptococcaceae, Clostridiaceae, and SMB53 (Lachnospiraceae) are the main butyrate producers [166,167], these alterations in microbial taxa affect gut homeostasis and participate in the pathogenesis of AMS. Beyond gastrointestinal symptoms, headache represents the most essential clinical hallmark of AMS. Recent studies on the gut–brain axis suggest that gut microbiota dysbiosis may contribute to hypoxia-related headache through neuroimmune and metabolic pathways [168–170]. Experimental evidence indicates that gut microbial imbalance can enhance migraine-like pain via TNF-α-mediated neuroinflammation [171]. Conversely, supplementation with SCFAs alleviates headache-like symptoms and intestinal barrier disruption in animal models [172]. Furthermore, systematic reviews have highlighted that microbial metabolites such as SCFAs and tryptophan derivatives influence trigeminal activation, neurovascular tone, and central inflammatory signaling [168,173]. Collectively, these findings suggest that gut dysbiosis-induced inflammation and altered metabolite signaling may underlie the headache manifestations of AMS via the gut–brain axis. Nevertheless, these associations remain largely correlative, as most studies rely on observational or cross-sectional designs. The relative contributions of diet, genetics, and hypoxia to these metabolic outcomes are difficult to disentangle. Longitudinal studies incorporating controlled dietary interventions and host genomic profiling will be essential to determine whether microbial remodeling truly mediates improved metabolic resilience at high altitudes.

High-altitude pulmonary and cerebral edema

High-altitude pulmonary edema (HAPE) and HACE represent the most severe and life-threatening forms of acute high-altitude illness. Both conditions are characterized by excessive vascular leakage in the pulmonary or cerebral circulations under hypobaric hypoxia, leading to rapid respiratory or neurological deterioration [174–176]. Although their pathogenesis has traditionally been attributed to hypoxia-induced pulmonary vasoconstriction and cerebral edema, emerging evidence suggests that gut microbiota dysbiosis and gut-derived inflammation may act as important contributing factors through systemic immune and metabolic signaling pathways.

The gut–lung axis plays a key role in HAPE. Under acute hypoxia, gut barrier integrity is compromised, leading to increased circulating LPS and systemic inflammation. These circulating microbial products stimulate alveolar macrophages and endothelial cells [177], inducing the release of pro-inflammatory cytokines such as IL-6 and TNF-α, which increase vascular permeability and contribute to pulmonary edema formation. Recent animal studies have demonstrated that gut opportunistic pathogens (e.g., Klebsiella pneumoniae and *E. coli*) can exacerbate hypoxia-induced lung injury by elevating lysophosphatidylcholines and promoting inflammatory responses [178]. Similarly, microbiota-derived metabolites can modulate lung gene expression and ameliorate hypoxia-induced pulmonary hypertension and injury by regulating anti-inflammatory and antioxidant pathways [179,180]. Collectively, these findings suggest that gut microbial homeostasis protects against hypoxia-induced pulmonary barrier dysfunction through immune and metabolic cross-talk.

The gut–brain axis may also participate in the development of HACE. Hypoxia and systemic inflammation increase blood-brain barrier permeability [181], allowing microbial metabolites and cytokines to affect cerebral endothelial cells and neurons. SCFAs such as butyrate and propionate are known to enhance blood-brain barrier integrity and suppress neuroinflammation [182–184], whereas their depletion under dysbiosis may predispose individuals to edema and neurological dysfunction. Reviews on the microbiota–gut–brain axis have highlighted that gut-derived immune mediators and metabolites (e.g., tryptophan catabolites, secondary bile acids) can influence central nervous system homeostasis through immune, endocrine, and vagal pathways [184–186]. Therefore, altered gut microbial composition and metabolic activity under high-altitude hypoxia may contribute to neurovascular injury and cerebral edema via inflammatory and metabolic signaling loops.

In summary, hypoxia-induced gut barrier damage and microbial dysbiosis may initiate systemic inflammation and vascular leakage that extend beyond the intestine to the lungs and brain. Future studies integrating microbiome, metabolomic, and host immune profiling in patients with HAPE and HACE will be critical to determine whether gut microbiota modulation can serve as a preventive or therapeutic strategy for these life-threatening conditions.

CMS

CMS is a clinical syndrome characterized by excessive erythrocytosis; cognitive impairment, pulmonary hypertension, and right ventricular hypertrophy often occur concurrently [187–189]. Weight loss, pulmonary hypertension, and cardiac hypertrophy are observed in rats with chronic hypobaric hypoxia, along with significant changes in the gut microbiota [98,179,190,191]. The relative abundances of

Bacteroides, *Parabacteroides*, *Alistipes*, and *Lactococcus* are increased in CMS, whereas that of *Prevotella* is significantly decreased, along with changes in microbial metabolites such as SCFAs and bile acids [98,191]. The gut microbiota aggravates systemic inflammation via the leakage of PAMPs and disturbances in SCFA production and bile acid metabolism. Faecal microbiota transplantation (FMT), probiotics, prebiotics, and synbiotics partially reverse these changes and improve ileal, cardiac, and pulmonary injury induced by chronic hypoxia [24,98,179,190,191]. In addition, chronic high-altitude exposure results in cognitive impairment, particularly in individuals residing above 4000 m or in immigrants, and the main manifestations are declines in psychomotor function, long-term memory, working memory, and language skills [192]. The gut microbiota promotes chronic inflammation and results in hippocampal neural damage, and the decreased absorption of L-valine due to gut barrier impairment leads to decreased levels of hippocampal glutamate and neurotrophic factors [193]. A significant decrease in *Clostridium* has been revealed in high-altitude Tibetans [27] as well as in high-altitude residents exhibiting cognitive impairment [193]. A decrease in *Clostridium* is related to an increase in L-valine in faeces, and gavage with *Clostridium* species improves cognitive behavior in mice by alleviating intestinal injury, L-valine absorption disorders, and hippocampal damage [193]. These findings demonstrate that gut microbial dysbiosis contributes to the development of CMS in high-altitude individuals via gut barrier impairment and chronic low-grade systemic inflammation. The causal direction between microbial dysbiosis and CMS pathology remains unresolved, as most evidence is associative and derived from animal or cross-sectional human studies. Future work integrating longitudinal clinical data with microbiome, metabolomic, and neuroimaging analyses will be critical to clarify whether microbial modulation represents a viable therapeutic target or a secondary consequence of chronic hypoxia.

Other diseases at high altitudes

Through the induction of chronic low-grade inflammation, gut microbial communities also participate in the pathogenesis of other diseases at high altitudes.

Irritable bowel syndrome has been found in 16.05% (13/81) of Han immigrants residing in high-altitude areas for 12 months, and symptoms are most severe at 6 months of high-altitude residence [194]. Entering high-altitude regions induce irritable bowel syndrome, but symptoms are gradually alleviated with prolonged residence. The variations in irritable bowel syndrome symptoms and stress response questionnaire scores are parallel, and the latter is correlated with the gut microbiota (e.g., *Alistipes*, *Parabacteroides*, etc.) [194]. On the one hand, the gut microbiota (e.g., *Alistipes*) produces neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid to modulate intestinal motility and visceral hypersensitivity via the enteric and central nervous systems [143,195]. On the other hand, mild mucosal and neural inflammation induced by hypoxia and microbiota remodelling promote the development of irritable bowel syndrome via gastrointestinal and emotional regulation [196]. Therefore, the gut microbiota participates in the pathogenesis of irritable bowel syndrome.

In addition, living at higher altitudes (> 2000 m) is a risk factor for colorectal cancer (prevalence: OR 1.6, 95% CI 1.52–1.68; mortality: OR 1.4, 95% CI 1.35–1.49) [197]. Oxidative stress and chronic inflammation drive colorectal cancer, and proinflammatory pathways such as the NF-κB, IL-23/Th17, and IL-6/STAT3 pathways are involved in its pathogenesis [198–202]. Notably, undifferentiated colonocytes (e.g., neoplastic cells and intestinal stem cells) rely on glycolysis for energy, and butyrate promotes proliferation in normal colonocytes but induces apoptosis and terminal differentiation in neoplastic colonocytes, a phenomenon known as the "butyrate paradox" [203]. Thus, a decrease in butyrate production might increase the risk of colorectal cancer.

Cholelithiasis, also known as "gallstones," is a common disorder in high-altitude areas, with a prevalence of 11.7%–20% [204,205]. Excessive cholesterol production, supersaturated bile, slow intestinal motility, and gallbladder inflammation promote the development of gallstones, particularly cholesterol gallstones [206]. The blood bile acid pool size and the concentrations of glycochenodeoxycholic acid and glycoursodeoxycholic acid are significantly decreased in individuals with cholesterol gallstones [207], which is similar to the changes reported in Han immigrants and native Tibetans [27]. The remodelled gut microbiota disturbs bile acid metabolism and biliary cholesterol secretion [208] and also triggers low-grade systemic inflammation, thereby increasing the risk of gallstones.

Moreover, an increase in altitude inhibits bone formation, promotes bone loss, increases the risk of osteoporosis [209,210], and delays bone age development in children [211,212]. Altitude is negatively correlated with the calcaneus quantitative ultrasound index, and gut microbial α-diversity indices and the abundance of *Catenibacterium* mediate this association [213]. The plasma total procollagen type 1 N-terminal propeptide, a specific marker for bone formation, was significantly increased in native Tibetans and was correlated with 50 species of the gut microbiota [27]. The gut microbiota modulates bone metabolism through multiple mechanisms, such as the absorption of nutrients (vitamin D and calcium) [214], local and systemic immune responses [215,216], and endocrine regulation (estrogen,

parathyroid hormone, etc.) [217,218]. For example, *Prevotella* maintains bone mass in mice by inhibiting the genesis and activity of osteoclasts and promoting osteogenesis [219,220], whereas *Blautia* induces bone loss in humans via chronic inflammation [221]. *Bifidobacterium longum* promotes fracture repair in aged female mice [222] and increases bone mass density via the upregulation of *Sparc* and *Bmp-2* gene expression in rats with ovariectomy-induced bone loss [223]. Therefore, the restructured gut microbiota might promote the development of osteoporosis and delay bone fracture repair in high-altitude individuals. Nevertheless, most current studies are associative and organ-specific, with limited integration across gastrointestinal, metabolic, and skeletal systems. It remains uncertain whether microbial alterations act as a primary driver or a secondary consequence of hypoxia-induced inflammation. Comprehensive multi-organ and longitudinal investigations are needed to delineate these interconnections and identify causal pathways.

Microbial therapeutics for mountain sickness

FMT

FMT, an evolving therapeutic option for many diseases, involves the transfer of faecal material from healthy donors to recipients to reconstitute a balanced gut microbial ecosystem [224,225]. Numerous formulations (capsule, lyophilized, frozen, and fresh) and delivery methods (colonoscopy, enema, nasoenteric tube, and oral ingestion) are available [226,227]. The intragastric administration of fresh faecal suspensions from plateau zokors increased the relative abundances of SCFA-producing Lachnospiraceae and Prevotellaceae in rats with chronic hypoxia, promoted weight gain, and reduced the feed conversion ratio, pulmonary arterial pressure, and right ventricular hypertrophy index [179,190]. Faecal SCFA and anti-inflammatory indole-3-lactic acid levels are significantly increased, thus alleviating intestinal and systemic inflammation and reducing the expression of proinflammatory genes (e.g., *IgE*, *IFN-γ*, and *TNF-α*) in the lung. Therefore, transplantation of the gut microbiota from plateau-adapted species could improve gut homeostasis and alleviate hypoxic pulmonary hypertension. In addition, gavage with fresh faecal suspensions from untreated rats partially reversed the changes in the gut microbiota (e.g., increases in *Bacteroides* and *Alistipes*) induced by chronic hypoxia and improved cardiac hypertrophy, such as the deposition of collagen fibers in the interventricular septum tissue and an increase in the collagen volume fraction [98]. Although it is far from clinical application, preliminary exploration has confirmed the efficiency of FMT in the prevention of CMS (Fig. 3). However, the translation of FMT into high-altitude medicine faces several challenges [228,229]. Current findings are largely limited to rodent models, and differences in host genetics, diet, and immune status may significantly affect microbial engraftment and therapeutic outcomes in humans. Moreover, the optimal dosage, frequency, and route of administration remain undefined for high-altitude disorders, where hypoxia and inflammation may alter microbial colonization efficiency. Importantly, safety concerns—such as potential infection transmission, dysbiosis-related immune reactions, and unpredictable host responses under hypoxic and immunocompromised conditions—must be rigorously evaluated before clinical application. Controlled preclinical studies and standardized donor-screening protocols are essential prerequisites for safely translating FMT into high-altitude interventions.

Probiotics, prebiotics, and synbiotics

Probiotics, prebiotics, and synbiotics (a combination of probiotics and prebiotics) can modulate the host immunity and metabolism and are considered safe and economical therapeutic options for many diseases [230,231]. Gut barrier impairment and intestinal dysbiosis play important roles in the development of high-altitude illness. *Lactobacillus rhamnosus* GG, stachyose, and synbiotics (a combination of both) increased the expression of epithelial cell junction proteins and transforming growth factor-β, elevated the activity of antioxidant enzymes (e.g., catalase), and reduced malondialdehyde, HIF-1α, and proinflammatory cytokines in the ileum to alleviate ileum injury induced by acute hypobaric hypoxia in mice [232]. The combination of *Lactobacillus rhamnosus* GG and stachyose reconstructed the gut microbiota, increased colonic SCFA levels, and effectively ameliorated oxidative stress and the inflammatory response [232]. Other probiotics (*Lactobacillus johnsonii* YH1136 isolated from a healthy Tibetan [233]) and synbiotics (*Faecalibacterium duncaniae* and inulin [234]; a symbiotic fermented whey beverage with *Brassica rapa* L. crude polysaccharide [235]; a commercially available composition with *Bifidobacterium* spp., *Lactobacillus* spp., *Saccharomyces boulardii*, *Streptococcus thermophilus*, and fructooligosaccharides [236]) also exhibited similar beneficial effects in alleviating intestinal damage induced by acute and subacute hypobaric hypoxia (7, 10, and 14 days) in mice or rats. These explorations highlight the potential of probiotics, prebiotics, and synbiotics for alleviating intestinal dysfunction and preventing AMS (Fig. 3).

During high-altitude acclimatization, the relative abundance of *Blautia* A increased significantly, whereas

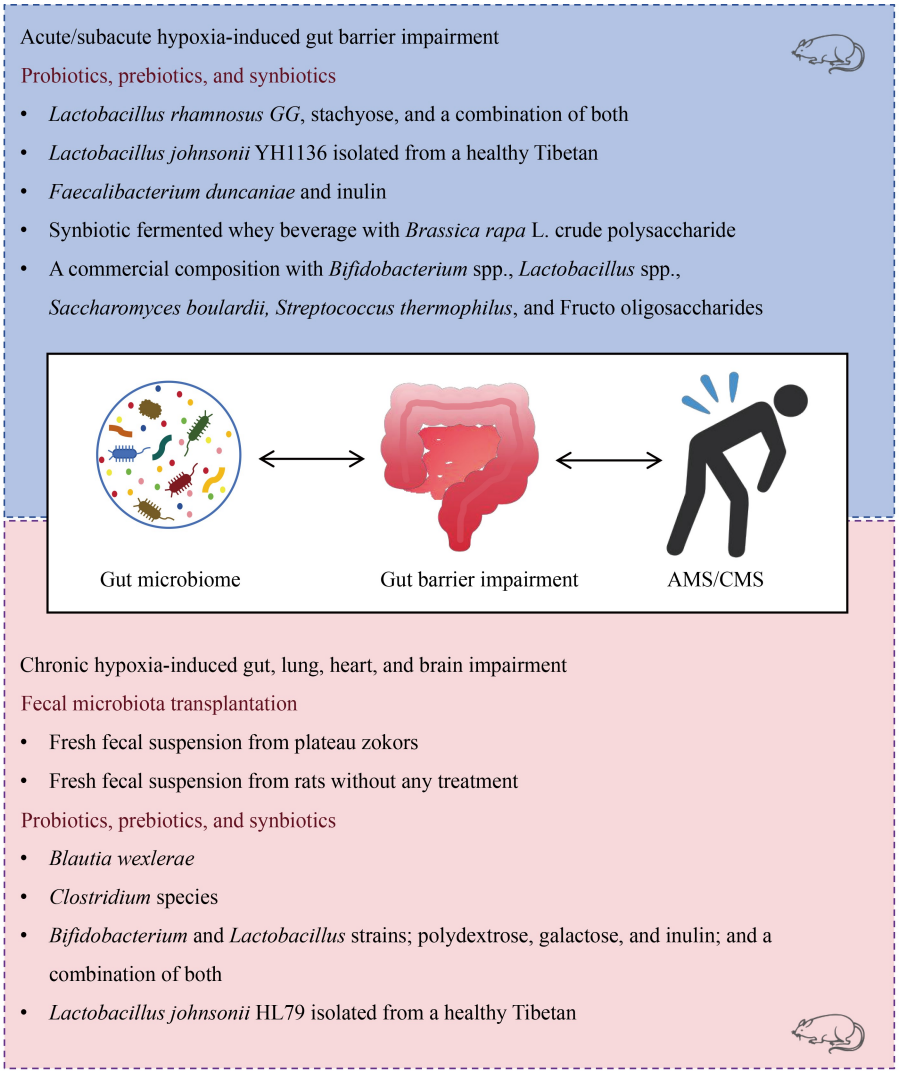

Fig. 3 Microbial therapeutic exploration for acute and chronic mountain sickness. Faecal microbial transplantation, probiotics, prebiotics, and synbiotics alleviate gut barrier impairment and multiorgan injuries (lungs, heart, and brain) induced by acute, subacute, and chronic hypoxia in animal models. Abbreviations: CMS, chronic mountain sickness; AMS, acute mountain sickness.

those of *Blautia wexlerae*, *Blautia obeum*, and *Blautia producta* decreased after prolonged residence [24,27]. Gavage with *Blautia wexlerae* alleviated hypoxemia, ileum injury, and lung injury (right ventricular systolic pressure, histological injury score, and collagen fiber deposition) induced by chronic hypoxia in mice [24]. In addition, the relative abundance of *Clostridium* species was significantly lower in high-altitude residents with cognitive impairment than in those without cognitive impairment [193]. Gavage with *Clostridium* species improved chronic hypobaric hypoxia-induced cognitive impairment in mice by increasing SCFA production, alleviating intestinal injury, reducing the levels of LPS and inflammatory factors in the serum and hippocampus, and improving intestinal L-valine absorption and hippocampal neurogenesis [193]. In addition, probiotics (*Bifidobacterium* and *Lactobacillus* strains), prebiotics (polydextrose, galactose, and inulin), and synbiotics (a combination of both) also partially reversed alterations in the gut microbiota characterized by *Prevotella* depletion and *Lactococcus* enrichment induced by chronic hypobaric hypoxia and improved cardiac hypertrophy (increased heart width and heart weight-to-body weight ratio) in rats [191]. Prebiotics and synbiotics also reversed the reduced expression of the cardiac myosin heavy chain alpha isoform and the increased expression of atrial natriuretic peptide, with synbiotics performing best [191]. Moreover, *Lactobacillus johnsonii* HL79 isolated from healthy Tibetans [237] reversed working memory impairment caused by 20-week hypobaric hypoxia in mice by reconstructing the gut microbial community and improving the antioxidant capacity of the blood and brain. These explorations demonstrate the potential of prebiotics, probiotics, and

synbiotics for both intestinal barrier restoration and CMS prevention (Fig. 3). Nonetheless, these promising results are predominantly derived from animal models and lack validation in human high-altitude populations. The variability in probiotic strains, dosages, and intervention durations across studies also limits comparability. Moreover, the efficacy and safety of probiotics under chronic hypoxic conditions remain uncertain, as oxygen tension, immune activation, and altered bile acid metabolism may influence bacterial viability and host interactions. Future randomized clinical trials should establish standardized dosing regimens, intervention timing (e.g., pre-exposure prophylaxis vs. long-term residence), and safety assessments to optimize microbial therapeutics for altitude-related disorders.

It is important to note that current authoritative clinical practice guidelines for altitude illnesses do not yet include specific recommendations for microbiome-based interventions [119,238,239]. This gap primarily reflects the relatively recent emergence of this field and the current lack of large-scale, randomized controlled trials specifically designed to validate the efficacy of microbial interventions. Compelling evidence links gut microbiome shifts to high-altitude health outcomes. Future rigorous investigations will be crucial for providing the evidence needed to update clinical practice guidelines, ultimately bridging the gap between mechanistic insight and actionable clinical recommendations for sojourners and residents on the plateau.

Conclusions and future perspectives

High-altitude regions feature extreme environments, and hypoxia—the core challenge—results in energy deficiency, oxidative stress, and inflammation. An impaired gut barrier permits microbial translocation and persistent PAMP exposure, driving the aggravation of local and systemic inflammation. In the initial phase, the gut microbiota enhances SCFA and secondary bile acid biosynthesis to restore the gut barrier and promote high-altitude acclimatization. However, after prolonged residence, the remodelled gut microbiota disturbs SCFA production and bile acid metabolism, thereby aggravating gut barrier impairment and affecting glucose and lipid metabolism. The gut microbiota participates in the pathogenesis of AMS, CMS, and other diseases at high altitudes (e.g., obesity, diabetes, irritable bowel syndrome, colorectal cancer, cholelithiasis, and osteoporosis). Preliminary explorations have confirmed the efficiency of microbial therapeutic options (FMT, probiotics, prebiotics, and synbiotics) in alleviating gut barrier impairment and multiorgan injuries induced by acute, subacute, and chronic hypoxia.

Although current studies have yielded valuable findings, several research gaps remain. First, substantial methodological heterogeneity exists across current studies, including differences in sequencing strategies (16S rRNA vs. shotgun metagenomics), targeted variable regions, reference databases, and bioinformatic pipelines, which collectively limit data comparability and reproducibility. In addition, inconsistent definitions of altitude thresholds (e.g., 2000 m vs. 5000 m) and variable exposure durations contribute to discrepancies in reported microbial diversity and community structure. These methodological variations must be considered when interpreting the existing evidence. Moreover, numerous confounding factors shape the gut microbiota [32,240] and should be controlled for in further real-world studies. Second, most existing data are derived from small-sample or animal studies, restricting statistical power and the ability to infer causality between hypoxia-induced microbial changes and physiologic outcomes. Future large-scale longitudinal cohorts and controlled human studies are needed to verify these associations. A large-sample longitudinal cohort study is necessary to assess the influence of altitude and the cumulative effect of time. Third, environmental and host-related variables, including diet, genetics, ethnicity, and lifestyle, differ substantially between populations and can mask altitude-specific microbial signatures. Therefore, standardized experimental protocols—including altitude classification, sampling strategies, and sequencing methodologies—are urgently needed to facilitate meta-analytic integration and reproducibility. In addition, research comparing immigrants with prolonged residence (e.g., several years) and aborigines is lacking, and relevant small-sample studies have produced contradictory results [28,29,35,36]. Aborigines are well adapted to extremely high-altitude environments, and comparisons between immigrants and aborigines can provide valuable insights. In addition, the present studies on microbial therapeutic options are all animal experiments, and further real-world verification is necessary. Ultimately, integrating standardized multi-omics analyses, host transcriptomics, and clinical phenotyping will be critical for defining causal links and translating microbiome discoveries into therapeutic strategies. The gut microbiota fundamentally regulates host health, and further exploration of its remodelling holds promise for developing options to promote high-altitude acclimatization and prevent high-altitude illness.

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Compliance with ethics guidelines

Conflicts of interest Yan Li, Mingshan Jiang, Jiangmei Pang, Chunxiang Ma, Hong Zhang, Fang Yin, Yongbin Jia, Xiang Zou, Tao Zuo, and Hu Zhang declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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