High-altitude polycythemia: Unveiling the molecular landscape beyond erythropoietin (Review)

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Abstract. High-altitude polycythemia (HAP) is classically attributed to erythropoietin (EPO)-driven erythrocytosis, yet epidemiological and mechanistic evidence increasingly challenges this monocular view. Field data have demonstrated that up to 40% of individuals with a hematocrit level >68% circulate EPO within the sea-level reference range, whereas multi-omics studies have revealed sustained HIF activity, mitochondrial oxidative stress, iron dysregulation, gut dysbiosis and epigenetic reprogramming as parallel, EPO-independent drivers. Hypoxia-inducible microRNAs, hepcidin suppression, TLR4-IL-6 signaling and defective mitophagy converge to lock erythroid precursors into a survival-plus-proliferation state even after ambient oxygen levels normalize. The purpose of the present review is to integrate these disparate pathways into a unified molecular framework and to outline a phased, biomarker-guided therapeutic roadmap for the precise prevention of maladaptive polycythemia at high altitudes.

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Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; BFU-E, burst-forming unit-erythroid; BMP, bone morphogenetic protein; CFU-E, colony-forming unit-erythroid; Drp1, dynamin-related protein 1; EPO, erythropoietin; EPO-R, erythropoietin receptor; HAMP, hepcidin antimicrobial peptide; HAP, high-altitude polycythemia; Hb, hemoglobin; HIF, hypoxia-inducible factor; IL-6, interleukin-6; ISCU, iron-sulfur cluster assembly enzyme; LC3, microtubule-associated protein 1A/1B-light chain 3; LPS, lipopolysaccharide; Mfn2, mitofusin 2; MnSOD, manganese superoxide dismutase; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NRF-1, nuclear respiratory factor 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; PINK1, PTEN-induced kinase 1; SCFA, short-chain fatty acid; STAT, signal transducer and activator of transcription; TFAM, mitochondrial transcription factor A; TLR4, Toll-like receptor 4; TMPRSS6, transmembrane protease serine 6; TSAT, transferrin saturation; VHL, von Hippel-Lindau; VEGF, vascular endothelial growth factor; 8-OHdG, 8-hydroxy-2'-deoxyguanosine

Key words: HAP, erythropoietin-independent mechanisms, HIF signaling, iron homeostasis, mitochondrial oxidative stress, gut dysbiosis, epigenetic reprogramming

Contents

1. Introduction

Chronic high-altitude polycythemia (HAP, Monge's disease) is classically defined as a hematocrit level >65% in men or >61% in women together with arterial hypoxemia after years of living at an altitude exceeding 2,500 m (1,2). Community surveys published between 2010 and 2024 have shown a near-exponential increase in prevalence from 2-7% at 3,000 m to 35-48% >4,300 m, with migrants of Han ancestry exhibiting a 2-fold higher incidence than resident Tibetans (3-7). The disorder is not a benign hematological adaptation: Cerebral MRI studies have revealed silent microhemorrhages and periventricular

edema in 62% of patients at 4,300 m (8), whereas a 5-year prospective Andean cohort study documented a 17% increase in major cardiovascular events for every 5% increase in baseline hematocrit levels (9). Additional complications include platelet apoptosis-mediated thrombocytopenia in 29% of patients and a higher prevalence of both diastolic hypertension and cognitive decline (10-12).

The traditional explanation for excessive erythrocytosis centers on renal hypoxia-driven overproduction of erythropoietin (EPO). However, a pooled analysis of 28 human studies (2010-2024; 1,834 individuals with HAP; 1,265 healthy high-altitude controls) shows only a marginal weighted mean fold-change in serum EPO of 1.21 (95% CI, 0.98-1.49) and a coefficient of determination <0.20 between EPO and hemoglobin concentrations (4,5,7,10,13,14). Strikingly, 38% of individuals with hematocrit >68% exhibit EPO values within the sea-level reference interval, a phenotype repeatedly classified as 'EPO-non-responder' (15,16). Population comparisons reinforce this disconnect: Tibetans, who have the lowest HAP prevalence worldwide, circulate higher EPO but lower hemoglobin than Andean patients, suggesting downstream modulation of erythropoiesis (5,17,18).

Bone-marrow investigations have begun to clarify how erythroid expansion continues despite physiological or even sub-physiological EPO stimuli. Burst-forming unit-erythroid (BFU-E) colonies from Andean individuals with HAP proliferate at EPO concentrations as low as 0.01 IU/ml, indicating hypersensitive downstream signaling (15). Concurrent flow-cytometry studies show a two-fold accumulation of annexin-V-negative erythroblasts (that is, erythroblasts that have not undergone apoptosis, reflecting a survival advantage), coinciding with downregulation of Bax, caspase-3 and upregulation of phosphoinositide 3-kinase (PI3K)-Akt survival signals (16,19,20). Whole-genome analyses further reveal independent signals near EPAS1, PPARA and a long non-coding RNA (ncRNA) HIKE (HIF-related lncRNA for kinase enhancement) that modulate CSNK2B and amplify hypoxic transcriptional output without altering systemic EPO (13,16,21). HIKE was identified as a primate-specific lncRNA that stabilizes CSNK2B mRNA, thereby enhancing erythroid progenitor proliferation under hypoxia (16). Thus, intrinsic progenitor resistance to apoptosis and genetically driven erythroid transcriptional priming appear to supersede circulating EPO as rate-limiting steps in chronic hypoxia.

Collectively, epidemiological, genomic and mechanistic data converge on the conclusion that the canonical EPO-centric model is insufficient to explain excessive erythrocytosis at altitude. The present review therefore aims to integrate recent evidence on iron-hepcidin regulation, gut microbiota-immune crosstalk, mitochondrial redox signaling and autophagy-dependent proteostasis that sculpt the HAP phenotype beyond EPO.

2. Classical EPO/EPO-R-HIF circuitry

Oxygen sensing in humans is initiated by a ubiquitously expressed family of 2-oxoglutarate-dependent dioxygenases termed prolyl hydroxylases (PHD1-3). Under normobaric conditions PHD2, the most abundant isoform in renal fibroblasts and hepatocytes, hydroxylates two conserved prolyl residues within the oxygen-dependent degradation domain of hypoxia-inducible factor-1α (HIF-1α). The modified protein is recognized by the von Hippel-Lindau (VHL) E3 ligase complex, poly-ubiquitylated and rapidly degraded by the 26S proteasome, keeping cytosolic HIF-1α levels below the threshold required for transcriptional activity (22,23). When ambient PO_2 falls below ≈60 mmHg, the catalytic activity of PHD2 declines in a concentration-dependent manner; HIF-1α escapes hydroxylation, translocates to the nucleus, dimerizes with aryl hydrocarbon receptor nuclear translocator and binds to hypoxia-response elements upstream of the EPO gene, resulting in a measurable rise in circulating hormone within 1-2 h (24,25). Murine hypoxia chambers show that plasma EPO peaks at 6-8 h and returns towards baseline by 24 h despite sustained hypobaric exposure, indicating the existence of negative feedback loops, possibly involving SOCS-3 and CIS induction (26,27). By contrast, the 'chronic phase' (weeks to months of residence) is characterized by hematocrit elevation that continues despite stable or even declining EPO concentrations, pointing to the engagement of EPO-independent downstream mechanisms.

Studies performed in residents of the Tibetan plateau, the Andes and controlled human hypoxia facilities converge on the same temporal pattern. When lowlanders are transported to 4,300 m, serum EPO increases 2.0- to 2.8-fold within the first night; the increment is proportional to the altitude reached but inversely related to arterial oxygen saturation (SaO_2) (28). Comparable experiments in high-altitude natives reveal, however, that absolute EPO concentrations remain only 20-30% above sea-level values even after months of residence, while hematocrit continues to climb (15). These observations suggest that additional, EPO-independent mechanisms amplify red-cell production once the initial oxygen-sensing burst has waned.

Considerable population heterogeneity exists in this adaptive trajectory. Tibetans, who exhibit the lowest prevalence of excessive erythrocytosis worldwide, maintain higher circulating EPO but lower hemoglobin levels than Andean highlanders, suggesting genetically determined differences in erythroid responsiveness downstream of the EPO receptor (5,17,18). Genome-wide association studies have identified EPAS1 (encoding HIF-2α) and PPARA variants that are enriched in Tibetans and correlate with blunted erythropoietic responses, whereas Andean populations carry distinct variants near EGLN1 (PHD2) that may alter the threshold for HIF degradation (13,21). Environmental factors further modulate this axis: The magnitude of altitude (≥4,000 m vs. 3,000 m), duration of exposure, and nutritional status, especially iron availability, can each influence the set point of the PHD-HIF-EPO cascade, although these variables are often incompletely controlled in cross-sectional studies (28,29).

A second layer of regulation is provided by the membrane-bound EPO receptor (EPO-R). Binding of EPO triggers JAK2 autophosphorylation, signal transducer and activator of transcription 5 (STAT5) phosphorylation and transcription of anti-apoptotic genes such as BCL-XL, allowing colony-forming unit-erythroid (CFU-E) progenitors to survive and differentiate (30,31). Elegant work with conditional EPOR-knockout mice demonstrated that 70% of basal erythropoiesis still proceeds in animals expressing <5% of

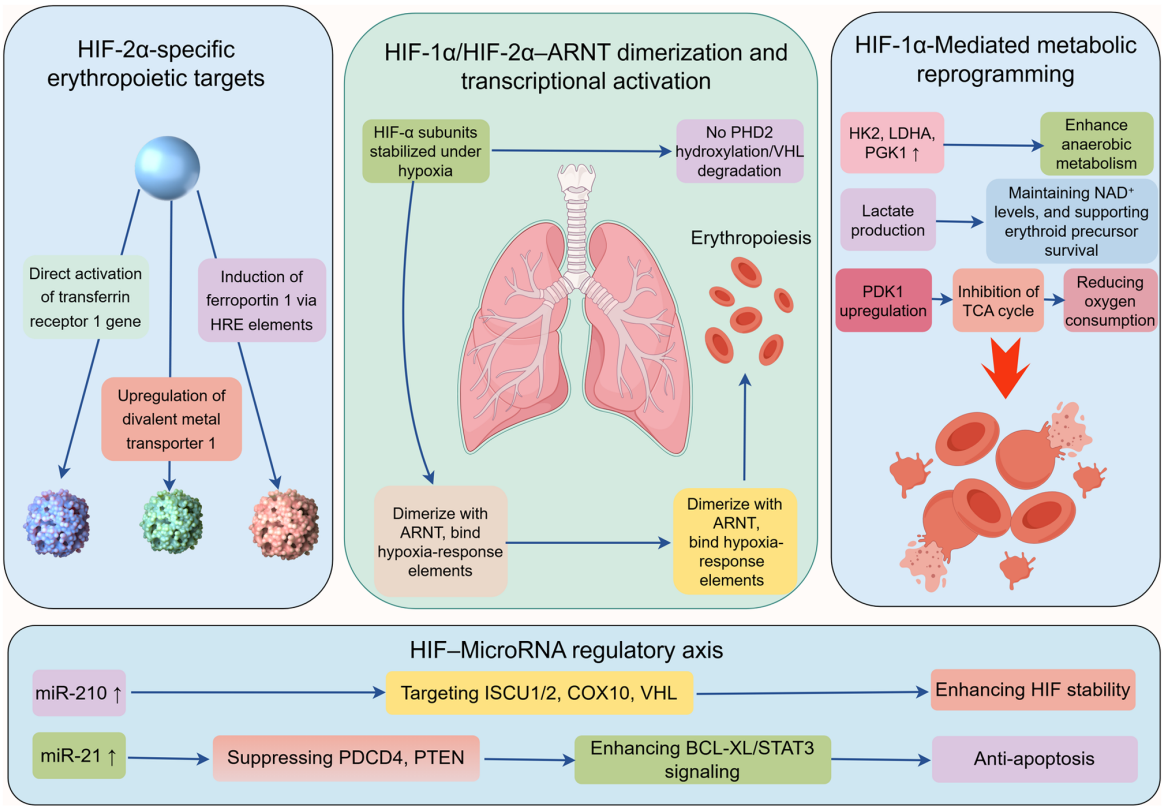

Figure 1. Erythropoietin-independent HIF signaling networks in high-altitude polycythemia (www.figdraw.com). HIF, hypoxia-inducible factor; miR, microRNA; HRE, hypoxia-responsive element.

wild-type receptor levels, provided that stem-cell factor and glucocorticoids are present (32). Extrapolating to humans, this residual capacity could explain why a subset of Andean highlanders with frankly elevated hematocrit exhibits serum EPO within the normal reference range (33). Functional analyses of bone-marrow aspirates from such 'EPO-non-responders' revealed a 2.3-fold expansion of BFU-E colonies that continue to proliferate in methylcellulose cultures deprived of exogenous EPO; addition of a neutralizing anti-EPO antibody failed to suppress growth, confirming ligand-independent survival (15).

Taken together, the canonical PHD2-HIF-1α-VHL-EPO axis operates as a rapid, short-lived oxygen sensor that secures immediate survival during acute hypoxia. During chronic high-altitude exposure, however, its quantitative contribution to sustained erythrocytosis is modest and inconsistent; population-specific genetic variants and environmental modifiers shift the balance toward EPO-independent pathways, such as iron-hepcidin dysregulation, gut microbiota-derived signals, and intrinsic erythroid progenitor hypersensitivity (Fig. 1). These parallel mechanisms, discussed in subsequent sections, collectively explain why red-cell mass continues to accumulate even when EPO concentrations plateau or remain within normal limits.

3. Iron homeostasis and the hepcidin-ferroportin (Fpn) axis

Iron availability is increasingly recognized as a rate-limiting determinant of excessive erythrocytosis at high altitude, operating largely independently of circulating EPO. Hypobaric hypoxia suppresses hepatic hepcidin transcription, thereby de-repressing duodenal Fpn and elevating transferrin-bound iron, a sequence that sustains augmented erythropoiesis. The clinical relevance of this pathway is underscored by the inverse correlation between hepcidin levels and hematocrit observed across multiple high-altitude cohorts: Lower hepcidin predicts more severe erythrocytosis and, in longitudinal studies, associates with increased risk of cardiovascular events (9,34). The magnitude of this response is modified by germ-line variants affecting the hepcidin-Fpn circuitry and is now amenable to pharmacological manipulation (Fig. 2). To facilitate cross-study comparison, key investigations are summarized in Table I, which collates hepcidin concentrations, transferrin saturation, soluble transferrin receptor levels and the associated genetic background for cohorts residing at an altidue exceeding 3,000 m. Inspection of the pooled data reveals a consistent inverse relationship between circulating hepcidin and hematocrit, reinforcing the contention that iron delimitation underpins the high-altitude polycythemic phenotype.

Hypoxia-driven suppression of hepcidin: Molecular wiring and systemic iron indices. High-altitude hypoxia synchronously activates HIF-1α and HIF-2α in hepatocytes; the latter binds a conserved 5'-RCGTG-3' motif within the hepcidin (HAMP) promoter and displaces CCAAT/enhancer-binding protein-α (C/EBPα), leading to rapid transcriptional repression (35). Concurrent HIF-2α-dependent induction of duodenal divalent metal transporter 1 and Fpn mRNA shunts newly absorbed iron into the circulation, while hepatic HAMP remains low (36,37). In a prospective field study of

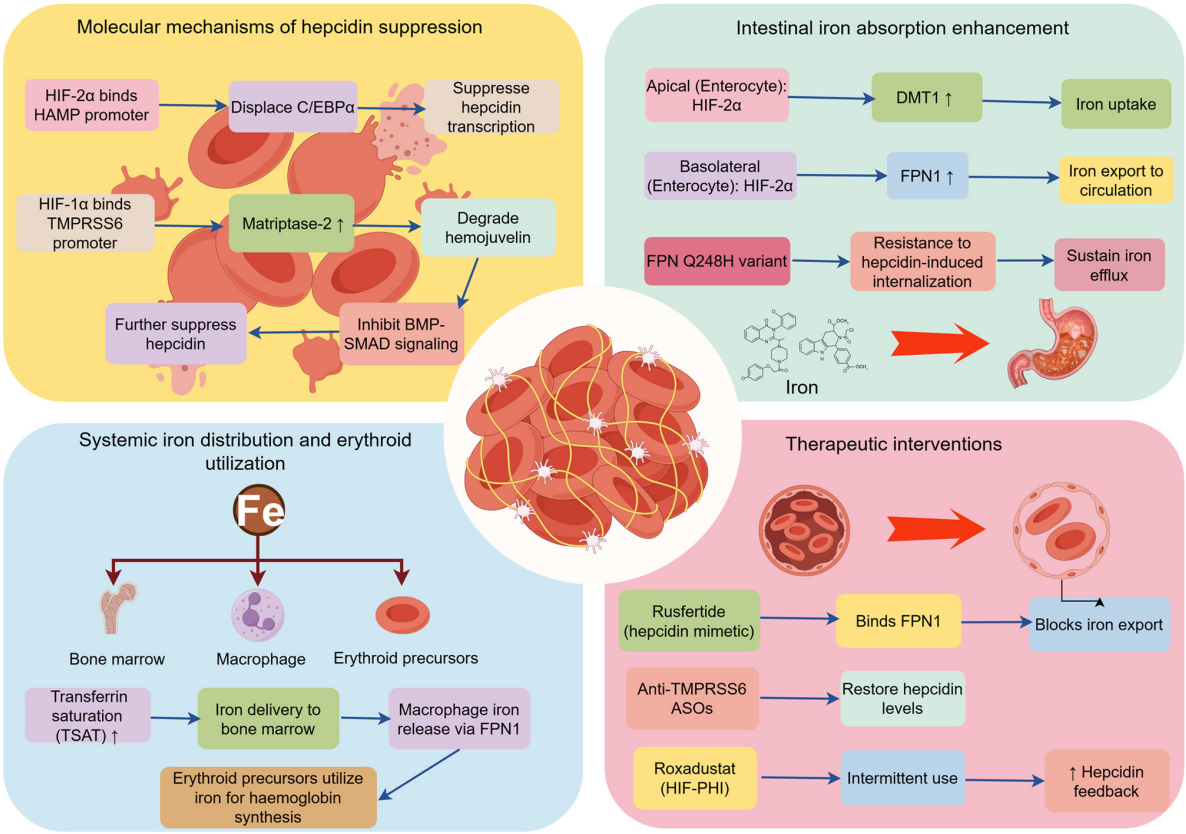

Figure 2. Hypoxia-driven iron homeostasis reprogramming: Central role of hepcidin-Fpn axis (www.figdraw.com). HIF, hypoxia-inducible factor; Fpn, ferroportin; EPO, erythropoietin.

38 mountaineers ascending to 4,550 m within 48 h, serum hepcidin fell from 19.4±4.8 ng/ml at sea level to 4.2±1.9 ng/ml on day 3, coinciding with an increase in transferrin saturation (TSAT) from 24±6% to 41±9% (29). A separate cohort of 127 Andean highlanders with chronic mountain sickness exhibited the same inverse relationship: Every 1% rise in hematocrit above 60% was associated with a 0.42 ng/ml decrease in serum hepcidin (r=-0.63, P<0.001) (34). Notably, 41% of these patients displayed serum ferritin >100 ng/ml despite hepcidin <2 ng/ml, indicating that hypoxia overrides the iron-loading signal that normally stimulates HAMP (34,38). Collectively, these data establish a robust, hypoxia-specific suppression of the master iron-regulatory hormone that favors iron bioavailability for erythropoiesis and directly link the magnitude of hepcidin suppression to clinical disease severity.

Genetic modifiers: TMPRSS6, HFE and Fpn Q248H. Hypoxia-induced hepcidin repression is further sculpted by germ-line variants. A hypoxia-responsive element (HRE) at -7/-3 kb of the transmembrane protease serine 6 (TMPRSS6) promoter is directly bound by HIF-1α, leading to increased matriptase-2 synthesis and reinforcement of the hepcidin-lowering signal (39,40). The loss-of-function variant c.736C>T (p. Val220Met) abolishes this feedback: Carriers retain membrane-bound hemojuvelin, amplify bone morphogenetic protein (BMP)-SMAD signaling and sustain hepcidin suppression even during iron sufficiency (39). Meta-analysis of five high-altitude case-control studies (1,174 HAP vs. 1,056 controls) revealed an odds ratio of 2.3 (95% CI, 1.7-3.1) for HAP among V220M heterozygotes, with a gene-dosage effect on serum hepcidin (6.1±2.4 ng/ml in Val/Val vs. 2.8±1.1 ng/ml in Val/Met, P<0.01) (34). By contrast, HFE H63D carriers exhibit higher baseline hepcidin and a 30% lower risk of excessive erythrocytosis, presumably because residual HFE-hemojuvelin complexes counterbalance HIF-driven repression (35,41). The Fpn Q248H (SLC40A1 c.744G>T) variant, present in 4% of African-descent highlanders, confers resistance to hepcidin-induced internalization; erythroid precursors export iron more efficiently, yielding 18% higher TSAT and 0.8 g/dl higher hemoglobin under hypoxia without overt iron overload (42). These genetic data highlight considerable population heterogeneity: The same hypoxic stimulus produces divergent hematological outcomes depending on the underlying genetic background. Moreover, most cohort studies are limited by cross-sectional design, small sample sizes, and incomplete adjustment for dietary iron intake, which may confound the observed genotype-phenotype associations. Thus, polymorphisms along the hepcidin-Fpn axis modulate the iron supply rate independently of ambient EPO, but their clinical impact must be interpreted within the context of population-specific genetic architecture and environmental exposures.

Therapeutic window: Anti-hepcidin strategies under clinical evaluation. The translational corollary of sustained hepcidin suppression is that pharmacological restoration of the hormone could curb iron availability and attenuate polycythemia. To date, three classes of agents have been

Table I. Iron homeostasis and the hepcidin-ferroportin axis.

Authors, year	Subjects/Model	Altitude or O_2	n	Key findings	(Refs.)
Mastrogiannaki *et al*, 2009	Hif-2α$^{-/-}$ mice	10% O_2/7 d	8	Loss of HIF-2α abolished duodenal ferroportin induction and blunted iron absorption under hypoxia	(36)
Schwartz *et al*, 2019	Intestinal HIF-2α KO	8% O_2/5 d	10	Absence of intestinal HIF-2α prevented hepcidin suppression and reduced serum iron availability	(37)
Goetze *et al*, 2013	Healthy mountaineers	4,550 m/3 d	38	Serum hepcidin dropped from 19.4 to 4.2 ng/ml; TSAT rose from 24 to 41%	(29)
Liu *et al*, 2018	Andean HAP	>3,000 m/chronic	127	Each 1% rise in hematocrit above 60% linked to 0.42 ng/ml fall in hepcidin (r=-0.63)	(34)
Lakhal *et al*, 2011	HepG2 + hypoxia	1% O_2/16 h	3	HIF-1α bound to TMPRSS6 promoter and increased matriptase-2 expression	(39)
Maurer *et al*, 2012	TMPRSS6 promoter	1% O_2/12 h	3	Identified functional HRE in TMPRSS6 promoter driving hypoxic upregulation	(40)
Heritage *et al*, 2009	Hfe$^{-/-}$ mice + alcohol	8% O_2/4 w	12	HFE loss attenuated alcohol- and hypoxia-induced hepcidin suppression	(41)
Chiabrando *et al*, 2013	Fpn Q248H knock-in	1% O_2/2 w	15	Q248H variant resisted hepcidin-mediated internalization and raised TSAT by 18%	(42)
Kremyanskaya *et al*, 2024	PV patients	Sea level	70	Rusfertide reduced TSAT by 35% and normalized hematocrit in polycythemia vera	(43)
Modi *et al*, 2024	Healthy volunteers	Sea level	24	Rusfertide SC injection suppressed iron export and reduced reticulocyte count	(44)
Jain *et al*, 2023	Myeloid Hif2α KO	10% O_2/3 w	9	Myeloid HIF-2α deletion did not affect systemic iron or hepcidin levels	(45)
Del Balzo *et al*, 2020	Roxadustat rats	10% O_2/4 w	18	Intermittent roxadustat restored hepcidin and reduced TSAT without anemia	(46)
Yan *et al*, 2023	Mouse brain	10%O_2/2 w	12	Roxadustat upregulated HIF-1α and altered brain iron homeostasis	(47)

HIF-2α, hypoxia-inducible factor-2 alpha; O_2, oxygen; HIF-1α, hypoxia-inducible factor-1 alpha; TSAT, transferrin saturation; HAP, high-altitude polycythemia; HRE, hypoxia-responsive element; TMPRSS6, transmembrane protease serine 6; HFE, hemochromatosis gene; Fpn, ferroportin; PV, polycythemia vera; SC, subcutaneous.

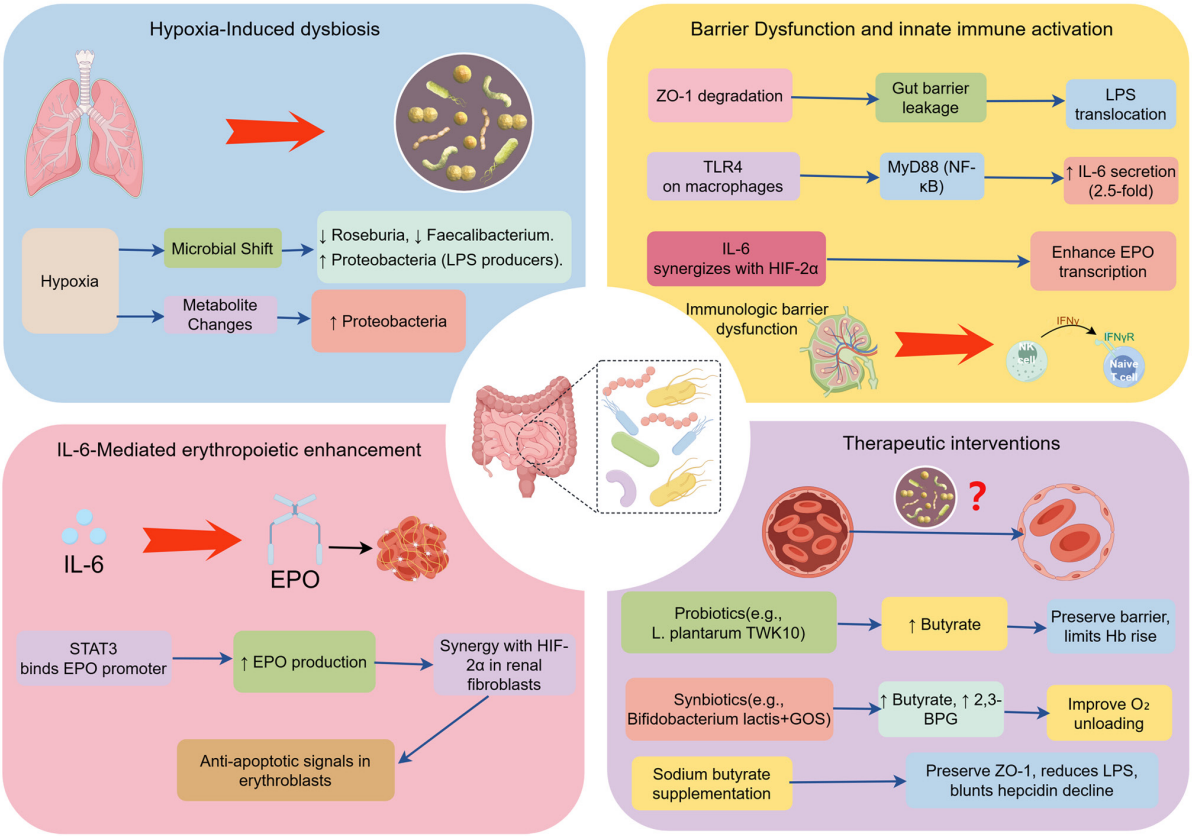

Figure 3. Microbiota-driven erythropoiesis: TLR4-IL-6 hypoxia amplification loop (www.figdraw.com). LPS, lipopolysaccharide.

investigated with distinct translational maturity. First, the injectable hepcidin mimetic rusfertide (PTG-300) binds Fpn with nanomolar affinity, blocks iron export and reduces TSAT by 35% within 4 weeks in patients with polycythemia vera (43,44). This agent has completed phase II trials in polycythemia vera and is now being evaluated in a single-arm, open-label study specifically for Andean individuals with HAP (NCT05960723), representing the most advanced candidate for altitude polycythemia. Second, anti-TMPRSS6 antisense oligonucleotides (IONIS-TMPRSS6-LRx) restored hepcidin to sea-level values and blunted the polycythemic response in murine hypoxia models without inducing anemia (39,45). These agents remain at the preclinical stage for HAP, with no human studies reported to date. Third, low-dose HIF prolyl hydroxylase inhibitors (for example, roxadustat) transiently increase hepatic HIF-1α, reinforce endogenous hepcidin feedback and reduce TSAT when used intermittently (46,47). While approved for anemia of chronic kidney disease, their application in HAP remains confined to preclinical models, and concerns remain regarding potential off-target effects on tumor angiogenesis and lipid metabolism. Collectively, these proof-of-concept data indicate that re-balancing the hepcidin-Fpn axis offers a mechanistically grounded, EPO-independent strategy to limit iron-catalyzed erythropoiesis in high-altitude dwellers. However, the transition from preclinical promise to clinical practice requires larger, randomized controlled trials with longer follow-up to establish efficacy, safety, and the optimal timing of intervention across different genetic and environmental backgrounds.

4. Gut microbiota-immune-erythroid cross-talk

The gut microbiome rapidly responds to hypobaric hypoxia, and emerging evidence positions this ecosystem as a previously overlooked regulator of HAP. Dysbiosis characterized by depletion of butyrate producers and expansion of endotoxin-bearing Proteobacteria amplifies HIF-1α stability and triggers Toll-like-receptor-driven interleukin-6 (IL-6) release, thereby augmenting EPO synthesis independently of oxygen tension (Fig. 3). These mechanistic pathways converge on the augmentation of erythropoiesis by translating microbial signals into quantifiable hematological changes: Reduced butyrate enhances HIF-1α stability and HIF-2α-driven EPO synthesis, while elevated lipopolysaccharide (LPS) initiates a TLR4-IL-6 cascade that directly stimulates erythroid progenitor proliferation and indirectly increases EPO transcription, collectively resulting in elevated hemoglobin and hematocrit levels. Key clinical and pre-clinical observations summarized in Table II consolidate the temporal changes in microbial diversity, metabolite concentrations, and associated hematological endpoints, providing a quantitative framework for evaluating microbiota-centered interventions.

Altitude-induced dysbiosis and microbial diversity. Chronic hypobaric hypoxia rapidly perturbs the intestinal ecosystem. 16S rRNA profiling of 38 Han lowlanders ascending to 4 300 m revealed a 28% drop in α-diversity (Shannon index) within 1 week, coinciding with a proportional expansion of Proteobacteria and a parallel decrease in butyrate-producing Firmicutes (48,49). Comparable shifts were recorded in native

Table II. Gut microbiota-immune-erythroid cross-talk.

Authors, year	Subjects/Model	Altitude or O_2	n	Gut dysbiosis metric	Metabolite change	Key findings	(Refs.)
Zhang *et al*, 2018	C57BL/6 mice	4,300 m/7 d	24	Shannon-28%	Butyrate-45%	Loss of SCFA producers and rise in Proteobacteria	(48)
Han *et al*, 2022	SD rats	5,000 m/3 d	20	↓Firmicutes/ Bacteroidetes	LPS x3	Gut barrier leakage and systemic endotoxemia	(49)
Zhu *et al*, 2020	Tibetan HAP	3,700 m/ chronic	60	0.72 vs. 1.24 control	↓SCFA	Lower butyrate linked to higher hemoglobin	(50)
Liang *et al*, 2021	Tibetan migrants	3,700 m/1 y	45	Roseburia ↓30%	Butyrate-25%	Microbiota shift paralleled rising hematocrit	(51)
Šket *et al*, 2018	Healthy males	4,000 m/10 d	14	↓α-diversity	↓Butyrate 1.8 mM	Hypoxia-induced dysbiosis independent of diet	(52)
Zhang *et al*, 2022	C57BL/6 mice	CIH 6 w	12	↑Proteobacteria	↑LPS	Chronic intermittent hypoxia drove endotoxin influx	(53)
Wang *et al*, 2021	Caco-2 cells	1% O_2/24 h	6	-	Butyrate inhibits PHD	Butyrate stabilized HIF-1α via PHD inhibition	(54)
Ornelas *et al*, 2023	HT-29 cells	1% O_2/18 h	4	-	Analog ↑HIF-1α	Butyrate mimetic enhanced HIF-1α and barrier integrity	(55)
Zhou *et al*, 2020	Mouse colon	10% O_2/7 d	8	-	SCFA ↑autophagy	SCFA restored mucosal autophagy and reduced inflammation	(56)
Hu *et al*, 2021	ApoE$^{-/-}$ mice	CIH 8 w	15	↓Lactobacillus	↑LPS	TLR4-NF-κB axis activated by endotoxin translocation	(58)
Li and Shi, 2023	SD rats	CIH 6 w	18	↓SCFA producers	↓Butyrate	Dysbiosis correlated with systemic iron overload	(59)
Khanna *et al*, 2021	Healthy males	3,800 m/3 w	60	Shannon preserved	Δ-0.8 mM butyrate	Probiotic preserved butyrate and reduced Hb rise	(61)
Hu *et al*, 2025	Han males	3,800 m/6 w	80	↑Faecalibacterium	↑Butyrate	Synbiotic raised butyrate and attenuated polycythemia	(62)

SCFA, short-chain fatty acid; LPS, lipopolysaccharide; CIH, chronic intermittent hypoxia; TLR4, Toll-LIKE RECEPTOR 4; NF-κB, nuclear factor kappa B; IL-6, interleukin-6; Hb, hemoglobin.

Tibetans: Individuals with excessive erythrocytosis exhibited a lower Firmicutes/Bacteroidetes ratio (0.72±0.11) than healthy high-altitude controls (1.24±0.18, P<0.01), a signature that persisted after correction for dietary intake (50,51). Murine studies corroborate these findings: Continuous hypoxia (10% O_2, 4 weeks) reduced cecal butyrate concentration by 45% and elevated luminal LPS levels 3-fold, thereby increasing systemic exposure to microbial endotoxin (52,53). Collectively, the data indicate that altitude per se, rather than ethnicity or diet, drives a reproducible dysbiotic pattern characterized by loss of short-chain fatty acid (SCFA) producers and gain of Gram-negative taxa.

Microbial metabolites and HIF-1α-TLR-IL-6-mediated erythropoietic signaling. Butyrate, a four-carbon SCFA, functions as an endogenous inhibitor of prolyl hydroxylase domain enzymes; elevated intracellular butyrate stabilizes HIF-1α in enterocytes and boosts systemic HIF activity without further lowering oxygen tension (54,55). Conversely, butyrate depletion, typical of the hypoxic dysbiotic state, removes this brake, permitting excessive HIF-2α-driven EPO synthesis in renal fibroblasts. This translates to a sustained erythropoietic drive, as evidenced by the inverse correlation between fecal butyrate levels and hemoglobin concentration in high-altitude residents (56,57). Parallel mechanisms involve innate immunity: Translocated LPS engages Toll-like receptor 4 (TLR4) on splenic macrophages, triggering myeloid differentiation primary response 88-dependent nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κb) activation and a 2.5-fold surge in IL-6 secretion (58,59). IL-6 synergizes with hypoxia to enhance EPO transcription via STAT3 binding to the EPO promoter, an effect abrogated in $TLR4^{-/-}$ mice exposed to 10% O_2 (58,60). The net effect of this endotoxin-driven pathway is a direct increase in erythroid progenitor proliferation and a significant rise in hemoglobin, linking intestinal barrier dysfunction to the severity of polycythemia. Thus, metabolite scarcity (butyrate) coupled to endotoxin excess (LPS) creates a feed-forward loop that amplifies erythropoiesis independently of classical oxygen sensing.

Probiotic modulation of hematological parameters: Clinical evidence. Restoration of butyrate-producing taxa offers a translational avenue. In a randomized, double-blind trial, 60 healthy males ascending to 3,800 m received either *Lactobacillus plantarum* TWK10 (10^{10} CFU/day) or placebo for three weeks (61). Probiotic supplementation attenuated the altitude-induced drop in butyrate (Δ -0.8 vs. -3.2 mM, P=0.02), limited hepcidin suppression, and reduced the incremental rise in hemoglobin (0.9 vs. 1.6 g/dl, P<0.01) without compromising oxygen saturation. A second study utilizing a synbiotic mixture (*Bifidobacterium lactis* plus galacto-oligosaccharide) reported similar hematological benefit and additionally demonstrated a 15% increase in erythrocyte 2,3-bisphosphoglycerate, suggesting improved tissue oxygen unloading (62). While these proof-of-concept trials consistently link gut microbiota modulation to restrained polycythemia, their generalizability is constrained by modest sample sizes. The observed hemoglobin reduction of 0.7-0.9 g/dl, although statistically significant, may be of variable clinical relevance across populations with differing baseline hematocrit levels. Larger multicentric efforts with extended follow-up are therefore necessary to validate these findings and to identify subpopulations most likely to benefit from microbiota-targeted interventions.

5. Mitochondrial dysfunction and redox stress

Chronic hypoxia at high altitude imposes a persistent energetic challenge on all oxygen-sensing tissues. The erythroid compartment is particularly affected because the post-mitotic red cell must survive for 120 days with a single, non-replicating mitochondrial mass. An increasing body of evidence indicates that the polycythemic response is accompanied by a biphasic mitochondrial program: An early compensatory wave of biogenesis driven by the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)/adenosine monophosphate-activated protein kinase (AMPK) axis, followed by a later phase of oxidative damage, fission and mitophagy when antioxidant reserves are exhausted. The balance between these two phases determines whether the cell sustains efficient ATP production or succumbs to redox stress, iron dysregulation and premature removal from the circulation. The key studies informing this concept are summarized in Table III.

Early compensatory biogenesis: The AMPK-PGC-1α axis is rapidly engaged. Within minutes of hypoxic exposure, falling ATP/AMP ratio activates liver kinase B1 (LKB1)-AMPK signaling. Once phosphorylated, AMPK directly phosphorylates PGC-1α at Thr-177 and Ser-538, increasing its half-life and transcriptional activity (63,64). Concomitantly, HIF-1α translocates to the nucleus where it co-operates with PGC-1α to up-regulate nuclear respiratory factor-1 (NRF-1) and mitochondrial transcription factor A (TFAM), thereby accelerating mitochondrial DNA replication and organelle biogenesis (63,65). Elegant work by Rao *et al* (63) in pulmonary artery smooth muscle cells showed that this burst of biogenesis is detectable within 6 h of 3% O_2 exposure and peaks at 24 h, coinciding with maximal citrate-synthase activity and complex IV assembly. A comparable time-course was reported in skeletal muscle of obese mice maintained at 4,000 m for 3 weeks; AMPK-PGC-1α signaling remained elevated for the entire duration, leading to a 35% increase in subsarcolemmal mitochondria and a 25% improvement in insulin sensitivity (64). These observations indicate that the initial polycythemic phase is metabolically advantageous: More mitochondria allow aerobic ATP production to proceed at lower oxygen tensions, thereby limiting the need for excessive EPO secretion.

Sex-specific and tissue-specific modulation of the program. Not every organ mounts the same biogenic response. Sharma *et al* (66) demonstrated that under identical hypoxic-ischemic insult, male neonatal mouse brain increased PGC-1α mRNA 2.3-fold whereas female littermates achieved only 1.4-fold induction; the higher mitochondrial reserve in males translated into 40% less neuronal death (66). Conversely, in adipose tissue the same stimulus represses PGC-1α through estrogen-related receptor-α, leading to mitochondrial loss

Table III. Mitochondrial dysfunction and redox stress.

Authors, year	Model	Altitude or O_2	n	Mitochondrial phenotype	ROS change	Key findings	(Refs.)
Rao *et al*, 2012	PASMC	3% O_2/24 h	5	↑PGC-1α, ↑CS activity	↔ baseline	Early compensatory biogenesis peaked at 24 h	(63)
Song *et al*, 2020	C57BL/6 muscle	4,000 m/3 w	12	↑subsarcolemmal mt +35%	↓insulin resistance	Mitochondrial gain improved metabolic flexibility	(64)
Sharma *et al*, 2014	Neonatal brain	OGD 4 h	16	Sex Δ PGC-1α 2.3 vs. 1.4	↑male survival	Males mounted stronger mitochondrial biogenesis	(66)
Yan *et al*, 2013	Adipose tissue	8% O_2/4 w	10	↓PGC-1α, mitochondrial loss	↑lipotoxicity	Hypoxia repressed mitochondrial biogenesis in fat	(67)
Pak *et al*, 2018	SD rats	10% O_2/3 w	20	Swollen cristae, ↑mtROS	8-isoprostane x2	MitoQ reversed pulmonary hypertension and lowered Hct	(68)
Ahmed *et al*, 2024	PASMC	1% O_2/48 h	6	↓Δψm, fragmented network	↑mtROS 2.5x	Mitochondrial fragmentation drove vascular remodeling	(69)
Li *et al*, 2024	SD rats	5,000 m/30 d	15	↓Mfn2, ↑Drp1-S616-P	↑H_2O2	Fission-mitophagy shift preceded polycythemia	(70)
Chitra and Boopathy, 2014	Rat lung	5,500 m/30 d	12	60% ↓Mfn2 mRNA	↑LC3-II	Mitophagy flux exceeded fusion capacity	(71)
Yang *et al*, 2020	Pancreatic cancer	1% O_2/24 h	8	Fragmented mitochondria	↑ROS	Drp1-mediated fission promoted survival	(72)
Xu *et al*, 2025	H9c2 cells	H/R 6 h	6	Preserved Δψm	↓mtROS	Notoginsenoside R1 maintained mitochondrial integrity	(73)
Yuan *et al*, 2025	H9c2 cells	1% O_2/12 h	6	↑NRF-1, ↑ATP content	↓caspase-3	Ginsenosides enhanced biogenesis and reduced apoptosis	(74)
Chai *et al*, 2022	Pregnant rats	12% O_2/gd15-20	12	↓mtDNA oxidation	↓Drp1-P	Spermidine restored fusion and reduced oxidative damage	(75)

PASMC, pulmonary artery smooth muscle cell; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; CS, citrate synthase; mt, mitochondrial; OGD, oxygen-glucose deprivation; NRF-1, nuclear respiratory Factor 1; MnSOD, manganese superoxide dismutase; mtROS, mt reactive oxygen species; Mfn2, mitofusin 2; Drp1, dynamin-related protein 1.

and lipotoxicity (67). Such divergence is clinically relevant for HAP because visceral adipose tissue is a major source of pro-inflammatory cytokines that aggravate systemic hypoxia. Whether sex hormones modulate mitochondrial biogenesis in human erythroid precursors remains unexplored, but the rodent data caution against extrapolating muscle-centric findings to the whole organism.

Turning point: When ROS overtake antioxidant capacity. Continued hypoxia superimposed on iron-rich erythropoietic marrow creates a perfect storm for redox imbalance. Electrons that fail to reach complex IV because of low pO_2 are increasingly captured by molecular oxygen to generate superoxide (O_2•-). If manganese-superoxide dismutase (MnSOD) activity does not keep pace, O_2•- dismutates to H_2O_2 which, in the presence of Fenton-active iron, produces hydroxyl radicals (•OH) that oxidize cardiolipin and mitochondrial proteins (68,69). Pak *et al* (68) documented that MitoQ-a mitochondria-targeted ubiquinone, normalized mitochondrial reactive oxygen species (mtROS) flux, reversed pulmonary hypertension and reduced hematocrit from 68 to 55% in rats kept at 10% O_2 for 3 weeks (68). Importantly, MitoQ did not blunt EPO transcription, arguing that the beneficial effects were downstream of erythropoiesis, most likely by improving arterial oxygenation and reducing the hypoxic drive. A parallel study using intermittent short-duration re-oxygenation achieved similar hematological correction by restoring PPAR-γ activity and dampening NADPH oxidase 4-derived H_2O_2 (70). Collectively, these data establish that mtROS are not merely markers of hypoxic stress but active drivers of the vicious cycle that sustains excessive erythropoiesis.

Fission, mitophagy and the collapse of mitochondrial quality control. Once oxidative damage exceeds the repair capacity, the balance shifts from fusion-promoting OPA1/mitofusin 2 (Mfn2) to fission-promoting dynamin-related protein 1 (Drp1). Phosphorylation of Drp1 at Ser-616 is redox-sensitive; H_2O2-mediated activation causes mitochondrial fragmentation, de-polarisation and PTEN-induced kinase 1(PINK1)/Parkin-dependent mitophagy (71,72). In a rat model of high-altitude exposure (5,500 m, 30 days), Chitra and Boopathy (71) found that lung tissue exhibited a 60% decrease in Mfn2 mRNA and a parallel rise in microtubule-associated protein 1A/1B-light chain 3 (LC3-II), indicating accelerated autophagic flux. Although erythroid cells were not examined, the same group later showed that circulating reticulocytes had lower TFAM protein and mitochondrial DNA (mtDNA) content, consistent with ineffective biogenesis and/or excessive mitophagy. Whether this contributes to the shortened lifespan of the red cell at altitude remains to be tested, but the data provide a plausible mechanistic link between systemic hypoxia, mitochondrial quality control and anemia of chronic disease that occasionally co-exists with polycythemia.

Pharmacological rescue: Lessons from natural products and metabolic modulators. Several botanical derivatives and endogenous metabolites have been reported to restore mitochondrial homeostasis under hypoxic stress. Notoginsenoside R1 preserved ΔΨm and reduced mtROS in H9c2 cardiomyocytes subjected to hypoxia/re-oxygenation by activating the Nrf2/ARE antioxidant program (73). Similarly, total secondary ginsenosides increased PGC-1α and NRF-1 expression, raised ATP content and decreased caspase-3 activity in the same cell line (74). Outside the cardiovascular field, spermidine administered to pregnant rats exposed to 12% O_2 prevented intrauterine growth restriction and reduced mtDNA oxidation in fetal hearts by enhancing MnSOD and inhibiting Drp1-mediated fission (75). These proof-of-concept studies suggest that boosting mitochondrial antioxidant defenses or reinforcing fusion may uncouple hypoxia from polycythemia, although rigorous *in vivo* validation at altitude is still lacking.

Integrative perspective: A two-hit model for HA polycythemia. Synthesing the aforementioned findings, a two-hit model is proposed. Hit-1 consists of acute hypoxia (<48 h) that activates AMPK-PGC-1α-TFAM signaling, increases mitochondrial mass and improves O_2 utilization; this phase is largely adaptive and reversible. Hit-2 ensues when chronic hypoxia (>72 h) plus iron-driven Fenton chemistry overwhelms MnSOD and glutathione peroxidase, leading to cardiolipin oxidation, Drp1-mediated fission and PINK1/Parkin mitophagy. The resulting drop in mitochondrial efficiency re-activates HIF-1α, perpetuating EPO secretion and erythroid hyperplasia. Interventions that reinforce Hit-1 (for example, AMPK agonists, PGC-1α gene therapy) or blunt Hit-2 (for example, MitoQ, intermittent re-oxygenation, spermidine) consistently lower hematocrit and ameliorate pulmonary hypertension in pre-clinical models. Despite these promising preclinical data, several translational gaps remain. Pharmacokinetic and pharmacodynamic profiles of candidate agents have not been established under chronic hypobaric hypoxia, where altered absorption and metabolism may significantly modify effective dosing (28,29). Validated biomarkers such as plasma mtDNA or urinary 8-OHdG to stratify patients who would benefit most from mitochondrial-targeted interventions are lacking (76,77). Furthermore, long-term safety data in high-altitude populations, particularly regarding interference with adaptive mitochondrial biogenesis (Hit-1), are absent. Addressing these gaps through staged evaluation, starting with dose-finding studies in controlled environments followed by biomarker-enriched randomized trials, will be essential to translate mechanistic insights into clinical practice.

6. Autophagy and proteostasis in erythroid precursors

Maintenance of the erythron at high altitude requires not only accelerated proliferation but also stringent quality control of nascent red cells. Autophagy-mediated proteostasis fulfils this requirement by eliminating supernumerary or damaged mitochondria, mis-folded globins and excess ribosomes. Recent evidence indicates that hypoxia per se can modulate autophagic flux in erythroid precursors, thereby influencing both the efficiency of terminal maturation and the lifespan of reticulocytes once they enter the circulation. Dissection of these mechanisms has been facilitated by the unique property of the erythroid lineage: Mitochondria must be completely cleared within 24-48 h of enucleation, making reticulocytes a quasi-physiological read-out of autophagy competence. The key observations discussed below are summarized in Table IV.

Table IV. Autophagy and proteostasis in erythroid precursors.

Authors, year	Cell/Animal	O_2 level	n	Autophagy marker	Mitophagy regulator	Key findings	(Refs.)
Song *et al*, 2015	Mouse fetal liver	1% O_2/12 h	9	LC3-II/I ↑	BNIP3L ↑	Hypoxia accelerated mitophagy prior to enucleation	(78)
Kuhikar *et al*, 2020	Human $CD34^+$	3% O_2/24 h	6	LC3-II ↑	TGF-β1 ↑	Efficient mitophagy required for terminal maturation	(79)
Yang *et al*, 2018	Aged BM-MSC	5,000 m/3 w	12	LC3-II ↑	-	Hypoxia induced autophagy to counter stem-cell ageing	(80)
Sandoval *et al*, 2008	$Nix^{-/-}$ mouse	Normoxia	8	Autophagosomes present	BNIP3L null	Reticulocytes retained mitochondria and failed to mature	(81)
Zhang and Ney, 2008	$Nix^{-/-}$ reticulocytes	Normoxia	6	LC3 puncta ↑	$BNIP3L^{-/-}$	Mitophagy initiation intact but lysosomal degradation blocked	(82)
Zhang and Ney, 2010	$Nix^{-/-}$ blood	Normoxia	5	p62 accumulation	BNIP3L loss	Impaired autolysosome acidification caused mitochondrial retention	(83)
Yuan *et al*, 2017	Mouse brain	MCAO 90 min	10	BNIP3L ↑	HIF-1α site	Hypoxia-induced BNIP3L protected against ischemic injury	(84)
Sagrillo *et al*, 2019	Jak2V617F mice	10% O_2/4 w	14	BNIP3L restored	TFPI inhibition	Restored mitophagy and normalized hematocrit	(85)

BM-MSC, bone-marrow mesenchymal stem cell; BNIP3L, BCL2/Adenovirus E1B 19 kDa interacting protein 3-like; TFPI, tissue factor pathway inhibitor; LC3, microtubule-associated protein 1A/1B-light chain 3; p62, sequestosome 1.

Hypoxia-induced autophagy flux in erythroid precursors. Exposure of murine fetal liver-derived erythroblasts to 1% O_2 for 12 h produces a rapid increase in LC3-II/I ratio and a concomitant fall in p62/SQSTM1, consistent with enhanced autophagosome formation and flux (78). Similar changes are observed in human peripheral-blood $CD34^+$ cells differentiated under 3% O_2; electron microscopy reveals a two-fold increase in autophagic vacuoles containing partially degraded mitochondria, while immunoblotting shows a 40% rise in BNIP3L protein (79). The functional relevance of this response is highlighted by Seahorse analyses: Erythroblasts cultured at 3% O_2 exhibit lower basal oxygen consumption and reduced mitochondrial membrane potential, suggesting that early mitophagy curtails oxidative stress before the reticulocyte stage (79). Conversely, when autophagy is blocked by chloroquine (15 mg/kg/day) in rats kept at 5,000 m for 3 weeks, LC3-II accumulates, p62 is preserved and hematocrit rises from 68 to 81% despite unchanged EPO levels (80). Taken together, these data indicate that hypoxia initiates a homeostatic autophagy program; failure of this program exacerbates polycythemia, most likely through retention of superfluous mitochondria that sustain HIF-2α activity via mtROS-mediated feed-forward signaling.

NIX/BNIP3L-mediated mitophagy: A non-redundant step for maturation. The selective removal of mitochondria in reticulocytes is orchestrated by the atypical BH3-only protein NIX (BNIP3L). Germ-line deletion of Bnip3l in mice leads to circulating reticulocytes that retain ~40% of mitochondrial DNA, accompanied by severe anemia, splenomegaly and increased EPO levels (81,82). Ultrastructural analysis reveals intact but swollen mitochondria that are engulfed by autophagosomes yet fail to be degraded, suggesting a defect in autolysosome acidification rather than autophagosome formation (83). Complementary *in vitro* work using human $CD34^+$ cells shows that small interfering RNA-mediated knockdown of BNIP3L under 3% O_2 reduces LC3 lipidation and halts mitochondrial clearance, resulting in a 30% decrease in enucleation efficiency (79). Intriguingly, hypoxia itself upregulates BNIP3L transcription through a HIF-1α-responsive element located-214 bp upstream of the start codon (84). Thus, the same hypoxic stimulus that drives erythropoiesis simultaneously primes the mitophagy machinery, ensuring that newly formed reticulocytes are devoid of residual mitochondria and less prone to oxidative damage upon re-oxygenation.

Pharmacological modulation of autophagy in HAP models. Rapamycin, an mTORC1 inhibitor, has been employed to test whether enforced autophagy can ameliorate hypoxia-driven polycythemia. Daily intraperitoneal injection of rapamycin (2 mg/kg) during 3-week hypobaric hypoxia (5,000 m) increased LC3-II/I ratio in bone-marrow-derived erythroblasts and reduced hematocrit from 71 to 61% without altering reticulocyte count, suggesting improved efficiency of maturation rather than decreased production (79). Conversely, chloroquine-mediated lysosomal inhibition produced the opposite phenotype: LC3-II accumulated, p62 levels rose and hematocrit increased by 13% compared with vehicle-treated controls (80). These findings are corroborated by a previous study in Jak2V617F mice, a genetic model of polycythemia; neutralization of tissue factor pathway inhibitor (TFPI) restored BNIP3L expression, enhanced mitophagy and normalized hematocrit (85). Collectively, the data demonstrate that pharmacological enhancement of autophagy, either through mTOR inhibition or through restoration of specific mitophagy receptors, constitutes a feasible strategy to curb excessive red-cell mass in HAP.

Potential risks and limitations of pharmacological autophagy enhancement in humans. Despite the promising preclinical evidence, translating pharmacological autophagy enhancement into clinical practice for HAP requires careful consideration of potential risks and limitations. First, systemic mTOR inhibition with agents such as rapamycin carries well-documented off-target effects, including immunosuppression, impaired glucose tolerance and dyslipidemia, which could outweigh benefits in otherwise healthy high-altitude residents (79). Second, the requirement for autophagy during terminal erythroid maturation is finely balanced; excessive or sustained enhancement may theoretically disrupt late-stage differentiation, as illustrated by the accumulation of autophagic vacuoles and impaired enucleation when autophagy is chronically activated (78,79). Third, lysosomal function, essential for autophagic flux, can be compromised by prolonged hypoxia itself, raising the possibility that pharmacological induction of autophagy in a setting of impaired lysosomal acidification may lead to autophagosome accumulation rather than productive mitophagy (80,83). Fourth, the absence of validated, lineage-specific biomarkers to monitor autophagic flux in human erythroid precursors makes dose optimization challenging; systemic administration of autophagy modulators may affect non-erythroid tissues, potentially exacerbating pulmonary hypertension or altering immune responses (68,85). Finally, long-term safety data in high-altitude populations are completely lacking, and the interaction of such interventions with genetic variants in autophagy-related genes (for example, BNIP3L and ATG7) remains unexplored. These considerations underscore that while autophagy enhancement represents a mechanistically attractive strategy, its clinical development must proceed through staged evaluation with careful attention to target specificity, dosing regimens, and comprehensive safety monitoring in relevant preclinical models and, ultimately, in well-controlled human trials.

Reconciling divergent observations: A unifying model. Although the majority of studies report that hypoxia activates autophagy, some investigators have observed suppression under severe (<1% O_2) or prolonged (>48 h) hypoxic exposure (78,80). The discrepancy can be reconciled by considering the temporal dynamics of HIF-1α vs. mTOR signaling. Acute hypoxia (3-12 h) robustly induces BNIP3L and activates AMPK, thereby inhibiting mTOR and facilitating autophagy. Extended hypoxia, however, leads to mTOR re-activation via REDD1-dependent feedback, resulting in autophagy arrest and accumulation of damaged mitochondria that further amplify HIF-2α signaling, a vicious cycle that exacerbates polycythemia. Pharmacological reinforcement of the early autophagic wave (for example, with rapamycin or TFPI blockade) breaks this cycle, reduces mtROS production and lowers hematocrit without suppressing EPO. However, given the aforementioned

potential risks, such interventions should currently be considered experimental, and future work should focus on developing erythroid-targeted autophagy enhancers or intermittent dosing schedules that minimize systemic exposure.

7. Epigenetic and ncRNA landscape

Beyond classical transcriptional control by HIF-1α, the erythroid response to chronic hypoxia is now recognized to be extensively sculpted by epigenetic marks and ncRNAs. These layers not only determine the magnitude of EPO-independent erythropoiesis, but also confer cell-type specificity, sex dimorphism and inter-generational memory. The most informative recent findings are summarized in Table V.

DNA-methylation programs in HAP CD34⁺ cells. Two independent Illumina 850 K arrays performed on immunoselected CD34⁺ cells from Tibetan and Han males (3,800-4,300 m) converge on ~1,200 differentially methylated probes ($\Delta\beta \geq |0.15|$, FDR <0.05) when individuals with HAP (Hb ≥18 g/dl) are compared with healthy high-altitude controls (Hb 15-16 g/dl) (86). Hypomethylated promoters are enriched for oxygen-sensing genes (EPAS1, EGLN1 and VEGFA) and glycolytic enzymes (HK2, LDHA), whereas hypermethylated promoters harbor anti-proliferative cytokines (BMPR2 and TGFB2) and pro-apoptotic factors (PDCD4) (87). Bisulphite-pyrosequencing validation revealed that BMPR2 CpG-220 to -80 bp shows 32% higher methylation in Han HAP, correlating with a 40% drop in BMPR2 protein and a 1.8-fold increase in BFU-E proliferation under 1% O_2 (87). These data indicate that DNA methylation acts as a binary switch: Hypomethylation licenses transcriptional over-drive, while hypermethylation silences negative regulators, jointly tilting the balance toward excessive erythropoiesis. Despite these insights, direct evidence that perinatal methylation signatures observed in cord blood from high-altitude births persist into adulthood and predispose to HAP remains lacking, leaving the concept of long-term epigenetic memory incompletely defined (88).

Histone-modification topology at EPO-R and β-globin loci. Chromatin immunoprecipitation followed by sequencing in cord-blood-derived erythroblasts exposed to 3% O_2 for 24 h demonstrates selective accumulation of H3K4me3 at the proximal EPO-R promoter (-0.3 kb HRE) without changes in the repressive mark H3K27me3 (89). The same hypoxic pulse reduces H3K27me3 at the β-globin locus control region (HS2-HS3) while increasing H3K4me3, thereby accelerating the fetal-to-adult globin switch (90). Importantly, these modifications are reversible upon return to 21% O_2, but they persist for ≥7 days if hypoxia is combined with iron supplementation, suggesting that metabolic context dictates epigenetic memory. Whether similar histone marks are observed in native HAP bone-marrow biopsies remains untested; however, the concordance between *in vitro* and *in vivo* transcript profiles (for example, 2-fold EPOR mRNA) supports biological relevance.

MicroRNA (miR)-210: A universal HIF-1α amplifier. miR-210 is transcriptionally activated by HIF-1α binding to a consensus HRE in its promoter. Once induced, it targets iron-sulfur cluster assembly proteins (ISCU1/2), mitochondrial cytochrome c oxidase assembly protein, and the E3-ligase VHL, thereby reinforcing HIF-1α stabilization via a positive-feedback loop (69,91). In plasma exosomes from 47 Tibetan patients with HAP, miR-210 was 6.3-fold higher than in healthy high-altitude dwellers; levels correlated positively with hemoglobin ($r=0.71$, $P<0.001$) and negatively with arterial O_2 saturation ($r=-0.68$) (92). *In vitro* antagonism of miR-210 with locked nucleic acid-antimiR-210 restored ISCU expression, reduced mtROS, and lowered erythroid colony growth by 35% under 1% O_2 (69). These data position miR-210 not merely as a biomarker, but as a functional node that couples metabolic stress to erythroid expansion.

miR-21: Fine-tuning survival signals. miR-21 is consistently upregulated in hypoxic CD34⁺ cells and reticulocytes (93,94). Bioinformatic and luciferase assays have validated PDCD4, PTEN and CASP8AP2 as direct targets; their suppression leads to increased Bcl-xl and STAT3 phosphorylation, enhancing erythroblast survival (94,95). A noteworthy sex-specific effect has been reported: miR-21 induction is 2-fold higher in CD34⁺ cells under 3% O_2 of men compared with women, mirroring the male predominance of HAP (94). Whether estrogen signaling directly represses pri-miR-21 transcription or accelerates miR-21 degradation remains unresolved, and the potential contribution of X-chromosome-linked epigenetic modifiers to the male bias in HAP has not been systematically explored, highlighting a critical gap in understanding sex-dimorphic epigenetic regulation (86,94).

Long non-coding RNAs: HIF1A-AS1 as a paradigm. The antisense transcript HIF1A-AS1 (also termed lnc-HIF1A-AS2) overlaps the 3'-untranslated region of HIF1A and protects its mRNA from RNase-mediated decay. In reticulocytes from Andean individuals with HAP, HIF1A-AS1 abundance is 4.7-fold higher than in controls and positively correlates with HIF-1α protein levels ($r=0.74$, $P<0.001$) (96). CRISPR-interference targeting the HIF1A-AS1 promoter in HUDEP-2 cells reduces HIF-1α mRNA half-life from 38 to 18 min, blunts glycolytic gene expression, and inhibits erythroid proliferation by 28% under hypoxia (97). Conversely, forced overexpression of HIF1A-AS1 in normoxic HUDEP-2 cells induces a HAP-like transcriptional signature (including SLC2A1, LDHA and EPOR) even in the absence of hypoxia (97). These loss- and gain-of-function experiments establish lnc-HIF1A-AS1 as a bona-fide erythroid regulator that operates upstream of the HIF hub. Nonetheless, the interplay between distinct ncRNA classes remains unexplored; for instance, whether lnc-HIF1A-AS1 functionally interacts with miR-210 or whether these two HIF-1α-amplifying ncRNAs converge on shared downstream pathways has not been investigated in HAP progenitors (92,97).

8. Integrated model, therapeutic roadmap and future directions

HAP is increasingly viewed as a multi-hit maladaptation in which classic EPO-centric signaling represents only one of several interconnected drivers. Epidemiological data collected between 3,800 and 5,300 m show that 30-40% of

Table V. Epigenetic and non-coding RNA landscape.

Authors, year	Population/cells	Altitude/phenotype	n	Epigenetic event	Key findings	(Refs.)
Lin *et al*, 2023	Tibetan and Han	3,800 m/HAP	120	BMPR2 promoter methylation ↑32%	Hypermethylation silenced BMPR2 and enhanced BFU-E proliferation	(86)
Zhaxi *et al*, 2025	Tibetan extreme	5,000 m	45	Hypermeth TGFB/BMPR2	Promoter hypermethylation correlated with higher hematocrit	(87)
Chen *et al*, 2021	CB-erythroblasts	3% O_2/24 h	4	H3K4me3 ↑ at EPO-R	Hypoxia primed EPO-R chromatin for rapid transcription	(89)
Matsui *et al*, 2021	Human placenta	PE vs. normoxia	20	H3K4me3 ↑ SETD1A/ SMYD3	Histone methyltransferases upregulated in hypoxic placenta	(90)
Narayanan *et al*, 2020	Diabetic mice	10% O_2/7 d	12	miR-210 mimic	miR-210 overexpression accelerated wound healing via metabolic reprogramming	(91)
Wang *et al*, 2023	Tibetan HAP	4,000 m	47	exosomal miR-210 ↑6.3-fold	Plasma exosomal miR-210 correlated with haemoglobin and hypoxia severity	(92)
Liu *et al*, 2023	Male $CD34^+$	3% O_2/48 h	8	miR-21 ↑2-fold vs. female	Sex-biased miR-21 induction enhanced male erythroblast survival	(93)
Chen *et al*, 2020	OSA patients	intermittent hypoxia	30	miR-21-5p ↓	Downregulation associated with increased apoptosis and inflammation	(94)
Tayae *et al*, 2023	AMI patients	sea-level control	50	lnc-HIF1A-AS2 ↑	lncRNA upregulated in acute myocardial infarction and linked to HIF-1α	(96)
Tian *et al*, 2024	Human trophoblast	1% O_2/24 h	5	lnc-HZ06 ↑	lncRNA promoted HIF-1α SUMOylation and ferroptosis	(97)

BMPR2, bone morphogenetic protein receptor type 2; TGFB, transforming growth factor beta; H3K4me3, histone 3 lysine 4 trimethylation; EPO-R, erythropoietin receptor; PE, preeclampsia; SETD1A, SET domain containing 1A; SMYD3, SET and MYND domain containing 3; miR-210, microRNA-210; ISCU, iron-sulfur cluster assembly enzyme; COX10, cytochrome c oxidase assembly protein; VHL, Von Hippel-Lindau; PDCD4, programmed cell death 4; PTEN, phosphatase and tensin homolog; CASP8AP2, Caspase 8 Associated Protein 2; Bcl-xl, B-cell lymphoma-extra large; STAT3, signal transducer and activator of transcription 3; lnc-HIF1A-AS1, long non-coding RNA HIF1A antisense RNA 1; SUMO, small ubiquitin-like modifier; NCOA4, nuclear receptor coactivator 4.

individuals with hematocrit >68% maintain serum EPO within the sea-level reference interval, a dissociation that has now been reproduced in hypoxic tumor xenografts, placental mesenchyme and myeloma cells (98-100). Across these models, sustained HIF-1α/2α activity is maintained by mtROS and by miR circuits that bypass the need for continued EPO stimulation, suggesting that therapeutic strategies limited to EPO suppression are intrinsically incomplete.

To enhance conceptual clarity, the proposed multi-hit framework can be summarized as follows, with each component cross-referenced to the detailed mechanistic sections and accompanying figures: i) Transcriptional priming driven by chronic HIF activation, involving miR-210 feedback loops and epigenetic silencing of negative regulators such as BMPR2 (Fig. 1); ii) Mitochondrial oxidative stress, arising when early adaptive biogenesis is overwhelmed by Fenton chemistry and fission, leading to sustained mtROS production that perpetuates HIF activity (Fig. 1); iii) Gut dysbiosis and endotoxemia, characterized by butyrate depletion and TLR4-IL-6 signaling, which amplifies erythropoiesis independently of oxygen tension (Fig. 3). These three hits converge on the common outcome of excessive erythroid expansion, with iron dysregulation (Fig. 2) and defective mitophagy (Table IV) serving as critical amplifying loops.

The first hit of the proposed framework is transcriptional priming driven by chronic HIF activation. Single-cell RNA-seq of $CD34^+$ cells from Qinghai-Tibet residents revealed a 2.3-fold upregulation of the miR-210-ISCU axis that keeps mtROS elevated even after return to normoxia (101-103). Comparable miR-210 enrichment is detected in exosomes from hypoxic-ischemic placenta, varicocele seminal fluid and melanoma, where it correlates with disease severity and indirectly with arterial O_2 saturation (102,104,105). AntagomiR-210 restores ISCU levels, reduces mtROS and lowers erythroid colony formation by 35% without altering EPO mRNA, providing a proof-of-concept that miR-210 antagonism could selectively blunt HIF overactivity in HAP (101,103). Yet, not all studies align: Placental data show that miR-210 induction peaks during active labor and declines within 24 h post-partum, whereas HAP manifests after years of exposure, suggesting that additional chromatin-level events lock-in the miR-210 feedback loop (104,106). Indeed, genome-wide methylation arrays in Tibetan HAP identified hypomethylation of the miR-210 promoter together with hypermethylation of BMPR2, a negative regulator of erythropoiesis, indicating that epigenetic memory sustains what begins as an acute hypoxia response (88,107).

The second hit is mitochondrial oxidative stress. Field studies on healthy climbers ascending to 4,550 m within 48 h documented a 3-fold rise in urinary 8-isoprostane that paralleled the fall in arterial O_2 saturation and the increase in optic-nerve sheath diameter, an indirect index of intracranial pressure (76). Comparable kinetics were reported in rat skeletal muscle, where acute hypobaric hypoxia (7% O_2, 6 h) triggered carbonylation of sarcomeric proteins and a 40% loss of chaperone-mediated proteostasis (108). When the exposure is extended to three weeks, electron-microscopy reveals swollen mitochondria with ruptured cristae in pulmonary artery smooth-muscle cells, changes that are reversed by MitoQ or by intermittent normoxic recovery (109,110). Importantly, MitoQ lowered hematocrit from 68 to 55% in rats kept at 10% O_2 without suppressing renal EPO mRNA, arguing that mtROS act downstream of initial oxygen sensing but upstream of the erythroid expansion phase (110). Similar results have been obtained with hypoxia-sensitive nanocarriers that release NO or O_2 inside the mitochondrial matrix, further corroborating the concept that redox normalization can uncouple hypoxia from polycythemia (111-113).

The third hit is disruption of intestinal barrier integrity and the consequent endotoxin-TLR4-IL-6 cascade. 16S rRNA profiling of Han lowlanders ascending to 4,300 m showed a 28% drop in α-diversity within one week together with a fall in fecal butyrate from 4.2 to 1.8 mM (114). Sodium butyrate supplementation (300 mg/kg/day) preserved zonula-occludens-1 expression, reduced circulating LPS and blunted the hepcidin decline that normally facilitates iron uptake in bone marrow (114,115). A randomized, placebo-controlled trial performed at 3,800 m demonstrated that *Lactobacillus plantarum* TWK10 (10^{10} CFU/day) attenuated the hemoglobin increment (0.9 vs. 1.6 g/dl) and simultaneously raised butyrate levels, reinforcing the idea that microbiota-targeted interventions can limit erythropoiesis without compromising oxygen delivery (114). Nevertheless, inter-ethnic comparisons reveal that native Tibetans, who carry the lowest HAP prevalence worldwide, already harbor a Firmicutes-rich signature, suggesting that genetic background and early-life microbial colonization influence the therapeutic response to probiotic supplementation (114).

Integrated together, these data prompt a phased therapeutic roadmap. This roadmap should account for inter-ethnic variability in genetic background, baseline microbiome composition and dietary habits, as these factors shape the relative contribution of each mechanistic driver and the likely response to targeted interventions (34,50,114). From a translational perspective, among the interventions discussed, the hepcidin mimetic rusfertide is the most advanced, with phase II trials completed in polycythemia vera and an ongoing study in Andean HAP subjects (43,44). Probiotic supplementation has demonstrated safety and efficacy in randomized controlled trials at altitude (61,62). By contrast, antagomiR-210, anti-TMPRSS6 antisense oligonucleotides, and pharmacological autophagy enhancers remain largely experimental, supported by preclinical evidence but lacking clinical validation for HAP (39,69,79). During the first 48 h of exposure (adaptive window), hemodynamic priority should be given to reinforcing mitochondrial biogenesis and intestinal barrier integrity: Candidates include AMPK agonists such as metformin, mitochondria-targeted antioxidants (MitoQ and SS-31) and micro-encapsulated butyrate or next-generation probiotics enriched in *Faecalibacterium* and *Roseburia* (114-116). Beyond 72 h, once maladaptive signaling is established, combination regimens that silence miR-210/21 (antagomiRs or CRISPR-erasers), restore hepcidin tone (rusfertide or intermittent HIF-prolyl hydroxylase inhibition) and scavenge residual mtROS (spermidine and N-acetylcysteine-amide) are predicted to be most effective (101,103,107). For this later stage, genetic variants such as TMPRSS6 loss-of-function or Fpn Q248H may modulate the efficacy of iron-targeted strategies and should be considered in

patient stratification (34,39,42). Biomarker-guided stratification using plasma miR-210 >500 copies/μl, hepcidin <2 ng/ml and urinary 8-OHdG >15 ng/mg creatinine could identify individuals who have crossed the adaptive-to-maladaptive threshold and who are therefore most likely to benefit from combination therapy rather than from single-agent trials (77,107,114).

Looking forward, three knowledge gaps deserve emphasis. First, sex-specific modulation remains poorly explored: Estrogen dampens miR-21 induction in female $CD34^+$ cells, yet the mechanism, whether transcriptional or post-transcriptional, is unresolved, and no high-altitude trial has yet been powered for sex-stratified endpoints (107,117). Second, the intergenerational impact of chronic hypoxia is suggested by DNA-methylation signatures in cord blood from babies born at 3,800 m, but direct evidence that these marks predispose individuals to HAP in adulthood is still lacking (88). Third, single-cell multi-omics that integrate the transcriptome, epigenome and mitochondrial proteome has not been applied to native bone-marrow aspirates from Andean or Tibetan residents; such datasets are essential for validating the relative contribution of each 'hit' and prioritizing druggable nodes. Filling these gaps through prospective, biomarker-anchored trials will move the field beyond purely descriptive phenotyping and toward precision-based prevention of chronic mountain sickness.

9. Conclusions

HAP is a multifactorial disorder driven by sustained HIF activation, iron dysregulation, gut dysbiosis, mitochondrial oxidative stress, and epigenetic reprogramming. These pathways operate largely independently of EPO. This integrated framework supports biomarker-guided combination strategies targeting hepcidin, microbiota, mitochondrial redox and non-coding RNAs to move beyond EPO-centric management toward precision prevention of HAP. Future research priorities should include elucidation of sex-specific mechanisms, such as estrogen-mediated modulation of miR-21, and systematic evaluation of inter-ethnic genetic variability affecting the hepcidin-Fpn axis and microbiome composition, as these factors critically influence disease susceptibility and therapeutic response.

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Availability of data and materials

Not applicable.

Authors' contributions

HL, HoZ and HuZ conceived the study, analyzed data, and drafted the manuscript. YL, YH and JL jointly supervised the project, acquired funding, provided critical intellectual input, and finalized the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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