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Review Article

Yak's Resilience and Adaptation to High-Altitude Stress

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Key words
Yak, High-Altitude, Stress, Resilience, Adaptation, *Bos grunniens*

ABSTRACT

Yaks, native to high-altitude regions, exhibit remarkable adaptations to the challenging environments they inhabit. Over generations, these robust animals have evolved various physiological, morphological, biochemical, and genetic traits through natural selection. These adaptations allow them to thrive in conditions characterized by low temperatures and oxygen pressure. Notable features include their thick, insulating coats, efficient respiratory systems, and specialized metabolism suited for high-altitude forage. Such unique evolutionary adjustments enable yaks to navigate the harsh terrains and limited resources of their high-altitude habitats, showcasing their exceptional resilience and suitability to these challenging ecosystems. Through extensive selective pressures over time, yaks have developed stable and distinctive genetic traits that facilitate their physiological, biochemical, and morphological adaptations to high-altitude environments. Consequently, yaks serve as a representative model for investigating mammalian adaptability to plateaus. The comprehension of these adaptive mechanisms offers unparalleled insights into evolutionary adaptations, with direct implications for the selective breeding of domesticated yaks. This review provides a comprehensive overview of the genetic adaptations in yak to the rigors of high-altitude environmental stress. Advances in genomics and theoretical frameworks have collectively illuminated the genetic underpinnings of high-altitude adaptations.

INTRODUCTION

The yak (*Bos grunniens*) is a native and scarce species of bovine found in the Qinghai-Tibet Plateau and surrounding areas, thriving at altitudes exceeding 2500 m (Wang *et al*., 2021). Referred to as the third pole, the Tibetan plateau constitutes the world's largest and highest year-round grazing expanse. This region is characterized by severe climatic conditions, including extreme cold, aridity, high ultraviolet radiation, and hypoxia, posing challenges to the survival of both humans and other mammals (Guo *et al*., 2021; Jiang *et al*., 2023). The yak, serving as an iconic representation of high altitudes and a vital resource for the Tibetan people, exhibits anatomical and physiological adaptations, a genetic foundation for mammalian adjustments, and a co-evolved microbiome that collectively prepare the animal for the challenges of high altitude and the harsh environment. However, the regulatory network governing this hypoxic adaptation remains unclear (Xin at al., 2022; Yang *et al*., 2022). Endothermic animals in these high-altitude regions face challenges due to reduced oxygen levels, which impact cellular functions and physiological performance. These mountainous areas are highly sensitive to climate change, posing a significant threat to biodiversity and the

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ecosystem (Ghatak *et al*., 2014). Furthermore, the cold climate, with temperatures dropping by approximately 6°C per kilometer in elevation, adds to the environmental harshness (Vuille, 2011). Other factors, such as late winter and early spring, food scarcity, and snow cover, contribute to severe malnutrition and weight loss among animals (Yang *et al*., 2022; Liu *et al*., 2023). Species in these extreme terrestrial environments have evolved unique characteristics through natural selection to adapt (Key and Sneeringer, 2014; Burtscher *et al*., 2018).

The yak holds significant importance in the lives and economic endeavors of the inhabitants residing in the extensive and challenging Qinghai-Tibetan plateau, as well as the surrounding mountainous areas (Shah *et al*., 2023). Yaks, the world's most remarkable domestic animals, thrive and reproduce in the challenging plateau environment (Miao *et al*., 2015). Domestication of yaks occurred more than 7300 years ago by early nomadic people, and they remain the only large animals coexisting with their wild ancestors in a similar environment (Qiu *et al*., 2015). Globally, there are over 17.6 million yaks, with the majority residing in the plateau regions of central Asia, covering approximately 2.5 million square kilometers around the Qinghai-Tibetan Plateau and adjacent highlands (Ma *et al*., 2013). From the very beginning, the domesticated yak, which traces its origins back to the wild yak, has been not just a primary source of sustenance for herders and their families but has also held a substantial role in shaping their culture, religion, and social interactions (Liu *et al*., 2023). Yaks provide essential resources (milk, meat, hair, hides, and manure) and services (draft, packing, and riding) to pastoralists and agro-pastoralists in these areas. Yaks also serve as pack animals, capable of covering distances of up to 15 km per day in high-altitude regions while bearing loads weighing up to 100 kg (Sapkota *et al*., 2022). They also hold financial and cultural significance, including status, dowry, and religious festivals (Liu *et al*., 2023). Yaks serve as a valuable model for studying natural and artificial selection in livestock domestication and adaptation to diverse environments.

The yak (*Bos grunniens*) is a characteristic ruminant species found on the Qinghai–Tibet Plateau (Wu *et al*., 2021). As the only bovine species native to the Qinghai-Tibetan Plateau and adjacent highlands, yaks exhibit exceptional adaptability to high altitudes, cold temperatures, low oxygen pressure, and prolonged periods of food scarcity (approximately half a year) (Ghatak *et al*., 2014; Liu *et al*., 2021; Wang *et al*., 2011; Lan *et al*., 2016). Natural and artificial selection has led to distinct yak breeds with unique morphological, physiological, and adaptability traits that enhance survival in harsh environments (Qiu *et al*., 2012; Zhang *et al*., 2016; Lan *et al*., 2018). Studying yak aerobic metabolism under hypoxic conditions offers insights into adaptive evolution (Ding *et al*., 2014). Combined with advanced molecular and genetic research, this knowledge forms the basis for investigating the genetic mechanisms related to adaptability to climate change, a current research focus (Yang *et al*., 2016; Friedrich and Wiener, 2020).

Altitudinal variations in physiological traits have been extensively studied across various species, and there is a relatively comprehensive understanding of physiological acclimation and acclimatization responses to hypoxia and cold exposure in endothermic vertebrates (Liu *et al*., 2023; Ding *et al*., 2020). However, it remains somewhat unclear how yaks residing on the Qinghai-Tibetan plateau have specifically adapted physiologically to the exceptionally low partial pressures of oxygen. Additionally, the increased metabolic cost of maintaining body temperature in the face of extremely low ambient temperatures is not clearly understood (Ayalew *et al*., 2021; Qiang, 2023). Understanding the mechanisms underlying adaptation to different agro-ecosystems is crucial for effective farm animal genetic resource management (Key and Sneeringer, 2014; Rojas-Downing *et al*., 2017). Intriguingly, multiple studies have focused on yak adaptation, allowing researchers to understand the morphological, physiological, biochemical, and genetic mechanisms of adaptation to extremely high altitudes (Qiu *et al*., 2012; Lan *et al*., 2016; Guang-Xin *et al*., 2019a; Wu *et al*., 2015; Guang-Xin *et al*., 2019b). Although research on the adaptation mechanisms of the yak in high altitudes has increased exponentially, review studies on the comprehensive, adaptive mechanisms remain scarce. Therefore, this review attempts to collate and synthesize current knowledge on the mechanisms of yak adaptation to high altitudes. Furthermore, it can also provide new avenues for in vitro and in vivo studies to further test hypotheses arising from previous investigations and options for designing and implementing interventions for improved yak productivity and resilience in high altitudes.

HOW YAKS ADAPT TO HIGH ALTITUDES

Altitude adaptation pertains to the capacity developed through natural selection in animals or plants, enabling them to thrive in plateau environments characterized by factors such as thin air, low oxygen content, intense ultraviolet rays, and low pressure over an extended period. The central aspect of altitude adaptation lies in the organism's ability to optimize the uptake and utilization of limited oxygen, ensuring the fulfillment of daily physiological processes in a low-oxygen environment (Xiang-Dong *et al*., 2019; Qiang, 2023). In recent years, there has been a growing interest in the mechanisms governing the adaptation of organisms to high-altitude environments, with yaks (*B. grunniens*) emerging as iconic symbols of the Tibetan Plateau (Ge *et al*., 2021a). High altitudes negatively impact the normal bodily functions of individuals, whether they are accustomed or unaccustomed to such environments. Mishra and Ganju (2010) reviewed environmental factors at high altitudes, such as cold and hypobaric hypoxia, which affect the immune system, making it more susceptible to conditions like cancer, infections, and autoimmune diseases (Mishra and Ganju, 2010). Inadequate hypoxia management affects reproduction and fertility traits, including reduced intrauterine growth in sheep (Parraguez *et al*., 2005) and impaired development and function of the corpus luteum (Parraguez *et al*., 2013). There should be an increased focus on breeding and managing animals for improved resilience to applied stressors (Colditz and Hine, 2016). To adapt to high-altitude environments, plateau-dwelling mammals have developed some distinct characteristics. The yak, a unique breed that inhabits the alpine pastoral area of the Tibetan Plateau, is one of the rare bovine breeds adapted to high altitudes and cold climates (Lan *et al*., 2016; Fu *et al*., 2014).

To cope with the challenges of high altitude, both humans and animals have undergone physiological and morphological adaptations to thrive in the harsh environment. Mammals, when exposed to high altitudes, display various physiological responses, such as an increased capacity for oxygen transport in the blood facilitated by improved hemoglobin function (Xiang-Dong *et al*., 2019; Li *et al*., 2022; Qiang, 2023). This enhancement enables a higher performance capacity, specifically the maximum oxygen consumption (VO_2 max), crucial for sustaining life in low-oxygen conditions (Ge *et al*., 2021b; Li *et al*., 2022). The genetic basis for high-altitude adaptation has been extensively investigated in humans and animals, including ruminants (Xin *et al*., 2021). In ruminants, the demanding conditions of high altitudes impact not just the host but also their commensal microbiota, particularly influencing the diversity and composition of the rumen microbiota. Numerous studies have explored the tripartite interactions among the host, environment, and rumen microbiota (Xin *et al*., 2021; Li *et al*., 2022). Comprehensive and thorough investigations into high-altitude adaptation have been conducted across various levels, including morphology, anatomy, hemodynamics, physiology, and genomics (Ge *et al*., 2021b).

YAK'S MORPHOLOGICAL ADAPTATIONS TO HIGH-ALTITUDE ENVIRONMENTS

Morphological adaptations refer to physical changes that occur over multiple generations in animals to enhance their adaptability to a specific environment. Yaks have evolved a range of morphological features that enhance their ability to thrive in high-altitude environments (Ayalew *et al*., 2021). These adaptations include enlarged lungs and heart optimizing their resilience in regions with lower oxygen levels, a shorter tongue improving their efficiency in food consumption amid challenging conditions, stronger environmental sensing aiding their adept navigation in high-altitude terrains, an elevated energy metabolism and the absence of hypoxic pulmonary vasoconstriction which distinguishes the yaks in their adaptation to the physiological challenges of high altitudes (Xin *et al*., 2020; Wang *et al*., 2021; Qiu *et al*., 2012; Sapkota *et al*., 2022). Over countless generations, the native high-altitude *B. grunniens*, despite their close relation to cattle, have successfully adapted to the chronic low-oxygen conditions of high altitudes. The exceptional adaptability of yaks to high-altitude environments is associated with the development of unique morphological mechanisms. Compared to their close relatives like cattle that inhabit lower altitudes, yaks have relatively larger lungs and hearts (Guan *et al*., 2017). Additionally, yaks have longer, wider, and rounder pulmonary artery endothelial cells with fewer smooth muscles, which enable better performance in high-altitude environments compared to cattle (Wang *et al*., 2006, 2021; Shao *et al*., 2010).

Heat conservation in yaks is achieved through a combination of factors, including a compact body, a dense outer coat of thick hair, and a fine undercoat during winter (Bao *et al*., 2021). The yak's resilience to cold is further supported by its compact physique, featuring a short neck, limbs, tail, small ears, and the absence of a dewlap. Both the male's scrotum and the female's udder are small and covered in hair. Additionally, the yak possesses a relatively small surface area per unit of body weight, limited sweat glands, and thick skin with non-functioning sweat glands. By autumn, a substantial layer of subcutaneous fat further contributes to thermal insulation. Oxygen uptake is facilitated by the yak's large lungs and heart, coupled with rapid breathing and hemoglobin characterized by a high affinity for oxygen (Wang *et al*., 2016; Xiong *et al*., 2020; Chen *et al*., 2022; Deng and Xu, 2021). The challenges of high-altitude environments go beyond hypoxia, as freezing temperatures and limited food supply contribute to their harshness. Yaks inhabit alpine regions at altitudes ranging from 3000 to 6000 meters, where there is no frost-free period throughout the year. Yaks are well-suited to this cold, high-altitude environment; they have compact bodies with reduced skin surface area per unit of body weight (0.016 m^2/kg). They lack functional sweat glands, which enhances their cold tolerance (Krishnan *et al*., 2016).

Moreover, the thick fleece covering their entire bodies helps conserve heat. This thick fleece consists of an outer layer of long hair and an undercoat composed of a dense layer of fine down fibers that appear during colder seasons to retain body heat and repel moisture (Weimer *et al*., 2009). Feeding mechanisms play a crucial role in the success and survival of vertebrate species in their environments (Shah *et al*., 2023). High-altitude alpine habitats are characterized by severe climates, short growing seasons, limited grazing resources, and challenging terrain, leading to severe malnutrition and weight loss among animals (Weimer *et al*., 2009; Long *et al*., 2008). Yaks have developed shorter tongues with greater lingual prominence, larger and more numerous conical papillae, and thicker keratinized epithelium compared to domestic cattle. These attributes enable yaks to consume a wider variety of pasture plant species (Shao *et al*., 2010). Additionally, yaks have an unusually large rumen relative to omasum, allowing them to consume large quantities of low-quality food and ferment it for an extended period to extract more nutrients during nutritional scarcity (Weimer *et al*., 2009).

Yaks exhibit exceptional adaptation to extreme cold conditions, demonstrating the ability to endure temperatures as low as -40°C. Their optimal performance occurs in environments where the average annual temperature remains below 5°C, and the average temperature during the warmest month stays below 13°C (Liu *et al*., 2021; Sapkota *et al*., 2022). The primary cold-resistant features of yaks include: (1) a compact body structure characterized by a short neck, limbs, and tail, coupled with small ears, resulting in minimal surface area for heat dissipation; the presence of a lengthy and dense outer hair layer on the chest, legs, and flanks, effectively trapping air against the body; and a dense yet fine undercoat of downy hairs (Guan *et al*., 2017; Deng and Xu, 2021). The outer hairs originate from primary hair follicles, while the downy coat is produced by secondary follicles. The ratio between these two types of follicles is highly seasonal, with a notable increase in secondary follicles during colder periods. It is crucial to emphasize that these adaptations primarily aim to minimize heat loss, as generating additional heat from winter forage would be energetically challenging. Despite these adaptations, yaks are susceptible to heat stress, exacerbated by the absence of functional sweat glands, with the limited sweating ability confined to the muzzle (Wang *et al*., 2021; Sapkota *et al*., 2022; Xin *et al*., 2020). The thick skin, sparse distribution of blood vessels, and low density of sweat glands in yaks contribute to their effective adaptation to cold environments at high altitudes. However, extended exposure to the hyperthermal environment typical at lower altitudes, and even in their natural habitat at high altitudes, can lead to heat stress (HS) and oxidative stress (Yang *et al*., 2022; Wu *et al*., 2021).

YAK'S PHYSIOLOGICAL ADAPTATIONS TO HIGH-ALTITUDE CHALLENGES

Physiology encompasses mechanisms and processes that enable organisms to cope with internal challenges (such as exercise, growth, and reproduction) and external stresses (such as variations in temperature, oxygen levels, water availability, salinity, pressure, radiation, and heavy metals). Yaks inhabit the entire Qinghai-Tibetan Plateau, and their physiological adaptations have played a crucial role in their ability to thrive in hostile environmental conditions (Wu *et al*., 2013). Chronic hypoxia is the primary stressor in high-altitude conditions, affecting the efficient functioning of the respiratory and cardiovascular systems in mammals and birds (Ivy and Scott, 2015).

Physiologically, high-altitude domesticated yaks have developed various strategies to adapt to chronic hypoxia. They are recognized for their pulmonary arterial resistance and a diminished capacity for vasoconstriction (Fang *et al*., 2020). These yaks possess numerous anatomical and physiological traits that equip them for life at high altitudes, including large lungs and hearts, predominant lignocellulose degradation and highly efficient energy metabolism (Qiang, 2023). In recent years, there has been widespread attention on the organic mechanisms that mediate adaptation to high-altitude environments. Genomes of mammals inhabiting highlands, including human highlanders, have been sequenced, revealing many genes associated with altitude adaptation. A focus on the mechanisms behind transcriptomic changes can offer insights into the adaptive evolution of other plateau species, including humans (Ge *et al*., 2021b). Yaks, owing to their prolonged colonization and widespread distribution on the plateau, serve as ideal models for studying adaptation to plateau environments. Compared with lowland cattle, yak lungs have developed physiological characteristics adapted to high-altitude hypoxia. These include a larger pulmonary alveolar area per unit, a thinner alveolar septum, a thinner blood–air barrier, and smooth muscles within the arteriole wall of microarteries with a diameter of < 50 mm features absent in lowland cattle. These physiological adaptations facilitate more efficient blood flow for oxygen transport under hypobaric hypoxia (Xin *et al*., 2021; Liu *et al*., 2023). The lung, a central functional organ in the respiratory system, plays a substantial role in adapting to hypoxia in plateau environments. In addition to enabling an animal's body to adapt to external environmental stimuli through a series of physiological changes, gene expression, as an intermediate phenotype linking DNA sequences and physiological traits, plays a crucial role in revealing molecular pathways/networks associated with genetic adaptation. There is growing evidence that changes in gene expression are also essential for adaptation to high altitudes (Wang *et al*., 2016; Ge *et al*., 2021b; Bao *et al*., 2021).

Interestingly, prolonged exposure to high altitudes increases the physiological response of yaks to chronic hypoxia. Yaks have a larger pulmonary alveolar area per unit area, thinner alveolar septum, thinner blood-air barrier, larger hearts and lungs, and higher concentrations of erythrocytes and hemoglobin than other cattle species (Guan *et al*., 2017). Thin-walled pulmonary arteries with minimal smooth muscle and the absence of right ventricular hypertrophy are additional hypoxic adaptations observed in yaks (Ding *et al*., 2014). These characteristics and changes in the cardiovascular system compensate for the hypobaric high-altitude environment (Fang *et al*., 2020). Hypoxia adaptation serves as a protective mechanism within the body, established to sustain fundamental life activities in high-altitude or specialized hypoxic working environments. This adaptive response addresses challenges arising from obstacles in the body's oxygen acquisition and transport, as well as hypoxia induced by various diseases. From a physiological perspective, hypoxia adaptation is characterized by a multi-system and multi-level coordination effect, manifesting as enhanced cardiovascular functions, increased oxygen-carrying capacity in the blood system, and greater efficiency in tissue oxygen (Bao *et al*., 2021; Ding *et al*., 2020).

This adaptation is likely a result of natural selection, which enhances the hypoxic pulmonary vasoconstrictor response, increasing red blood cell production and hemoglobin concentrations in yaks (Ding *et al*., 2014). Research has shown that chronic exposure to hypoxic conditions leads to an increase in blood/erythrocyte volume in high-altitude native animals, facilitating oxygen delivery to tissues through hyperventilation, hemoconcentration, and stimulated erythropoiesis (Xin *et al*., 2021; West, 2015, 2017).

Adaptation often comes at the cost of performance, and animals with lower performance often have better survivability due to lower input requirements, especially in terms of feed, and moderate internal heat production (Gaughan *et al*., 2019). In their natural habitat, yaks must maintain normal energy production under hypoxic conditions (Wang *et al*., 2011), optimize nutritional assimilation due to cold stress (Fang *et al*., 2020), and cope with limited feed resources (Shah *et al*., 2023). To combat cold stress, yaks employ peripheral vasoconstriction to prevent heat loss, along with heat production through mechanisms such as shivering and uncoupled mitochondrial activity (Manou-Stathopoulou *et al*., 2015). Additionally, many cold-adapted species can temporarily reduce their metabolism in response to harsh environmental conditions, leading to torpor or, in extreme cases, hibernation (Ruf and Geiser, 2015). Yaks exhibit a significant reduction in heat production during winter, likely due to their adaptation to low oxygen concentrations in the air, the cold environment, and prolonged undernutrition during the six-month-long cold season of the Tibetan plateau (Jiang *et al*., 2023).

BIOCHEMICAL ADAPTATIONS FOR HIGH-ALTITUDE SURVIVAL IN YAKS

There are limited reports on heat stress (HS) in yaks raised at low altitudes during high-temperature seasons. Recent studies have indicated the involvement of oxidative stress in the mechanisms underlying animal stress (Wu *et al*., 2021; Zhang *et al*., 2022). Certain free amino acids (AAs) exhibit antioxidant properties as a response to HS. Additionally, free fatty acids (FFAs) and other nutrients are utilized for oxidative phosphorylation to address the negative energy balance in animals experiencing HS. In the context of heat stress conditions, the levels of circulating AAs, FFAs, and other nutrients may undergo alterations as part of thermal adaptation (Yang *et al*., 2022; Khan *et al*., 2023; Huang *et al*., 2022; Fan *et al*., 2020).

The cold, hypoxic conditions of high-altitude habitats impose severe metabolic demands on endothermic vertebrates. Understanding how high-altitude endotherms cope with the combined effects of hypoxia and cold can provide important insights into the process of adaptive evolution. Biochemical adaptations offer fascinating insights into how organisms' function and evolve to maintain physiological processes under a wide range of environmental conditions. Yaks exhibit remarkable biochemical adaptations that enable them to thrive in the challenging environment of the Qinghai-Tibetan plateau, characterized by altitudes exceeding 2000 m (Bao *et al*., 2021; Shah *et al*., 2023). One of the key adaptations is their high blood hemoglobin concentrations, which enable them to tolerate the low atmospheric partial pressures of oxygen at high altitudes. The lower energy metabolism observed in yaks may result from their adaptation to the low oxygen concentration in the air, the cold climate, and the prolonged period of undernutrition during the annual six-month-long cold season of the Qinghai-Tibetan plateau. Yaks rely on their rumen microorganisms to ferment approximately 70-80% of their feed intake, producing volatile fatty acids that provide 60-75% of their required metabolic energy. This phenomenon may represent a coevolutionary strategy to cope with the limited feed resources in cold environments (Zou *et al*., 2019).

In comparison to indigenous cattle, yaks exhibit a lower rate of urinary nitrogen excretion, possibly as an adaptation to cope with poor feed availability, and a more efficient utilization of nitrogen. This efficiency is partly attributed to a greater microbial protein production in the rumen (Zhou *et al*., 2017), believed to contribute to the rapid recovery of body weight during the summer grazing period (Wang *et al*., 2009). Additionally, the yak's low maintenance protein requirements and reduced body surface area result in a lower metabolic rate, collectively contributing to their survival in the challenging environmental conditions of the Tibetan plateau. While there are variations among species, many studies attribute metabolic adaptation to high altitudes to a decreased muscle oxidative capacity. In this context, lactate dehydrogenase (LDH) plays a crucial role in anaerobic glycolysis by catalyzing the conversion between pyruvate and lactate, a pivotal process in energy metabolism (Huang *et al*., 2022). Interestingly, unlike cattle, yaks exhibit higher LDH activities in the longissimus muscle, facilitating carbohydrate utilization under limited oxygen supplies. This unique adaptive feature underscores the remarkable capacity of yaks to thrive at high altitudes (Lin *et al*., 2011). The evidence that high-altitude yaks in the study area exhibit minimal increases in hemoglobin content, compared to their counterparts at relatively lower altitudes, even when both are above 3000 meters above sea level, implies a specific adaptation to the hypoxic environment. In this context, yaks residing at high altitudes seem to have undergone genetic adaptation to the elevated environment, primarily by eliminating the hypoxic pulmonary vasoconstrictor response in the absence of a hypoxemic stimulus to stimulate red blood cell production and increase hemoglobin concentrations (Ma *et al*., 2022; Jiang *et al*., 2023; Fang *et al*., 2020).

GENETIC RESISTANCE: YAK ADAPTATION TO HIGH-ALTITUDE ENVIRONMENTS

Genetic adaptations to new environments and climate changes are crucial for the survival of species. The genetic mechanisms behind high-altitude adaptation are highly complex (Gnecchi-Ruscone *et al*., 2018; Zhang *et al*., 2022). Recent advancements in the genomic analysis of yaks have created exciting prospects for delving into the molecular genetic foundations of adaptive physiological traits. Genes undergoing positive selection and rapid evolution in the yak lineage have been observed to exhibit significant enrichment in functional categories and pathways associated with hypoxia stress and nutrition metabolism (Jiang *et al*., 2023; Xin *et al*., 2020; Kour *et al*., 2022). Long-term selection has led to the development of unique characteristics in species to cope with extreme terrestrial environments (Key and Sneeringer, 2014; Burtscher *et al*., 2018). Genetic variation within a population is essential for adaptability and species evolution over time (Yan *et al*., 2023). Adaptive traits often result from multiple genetic mutations, making them challenging to detect (Pritchard and Di Rienzo, 2010). Natural selection can occur through selective sweeps at specific genetic loci or simultaneous shifts in allele frequencies at multiple loci (Hollinger *et al*., 2019). Advances in sequencing and genotyping technology have facilitated the identification of genomic features related to livestock adaptation. In yak populations, several genes associated with high-altitude adaptation have been discovered, primarily linked to responses to hypoxia, temperature acclimatization, cardiovascular system modification, and energy metabolism (Qiu *et al*., 2012; Guang-Xin *et al*., 2019a; Ding *et al*., 2019).

One key gene that plays a pivotal role in high-altitude adaptation is the endothelial PAS domain-containing protein 1 (EPAS1) gene, which encodes the hypoxia-inducible transcription factor (HIF-2α). This gene regulates erythropoietin production in response to oxygen levels in high-altitude environments (Qiu *et al*., 2012; Wu *et al*., 2015; Dolt *et al*., 2007). Another crucial gene is the vascular endothelial growth factor-A (VEGF-A) gene, responsible for regulating angiogenesis and blood vessel size during high-altitude adaptation (Wu *et al*., 2013). Yaks must maintain normal energy production and optimize nutritional assimilation due to the limited availability of forage resources in high-altitude environments (Yang *et al*., 2022; Wang *et al*., 2011; Xiong *et al*., 2020).

Qiu *et al*. (2012) identified five key genes that undergo positive selection in yak nutritional and metabolic pathways. Among these genes, the Camk2b gene stands out as it regulates gastric acid secretion in the rumen, aiding in the assimilation of volatile fatty acids produced during ruminal fermentation (Yang *et al*., 2022; Wiemer *et al*., 2009). Additionally, genes such as Gcnt3, AQP4, DCC, GSTCD, ND1, Hsd17b12, GRIK4, IFNLR1, Whsc1, and Glul play essential roles in polysaccharide, fatty acid, and amino acid metabolism, respectively (Li *et al*., 2009; Ding *et al*., 2020; Wang *et al*., 2017, 2019; Shi *et al*., 2017; Guang-Xin *et al*., 2020). Likewise, Ma *et al.* (2022) reported EPAS1, EGLN1, and PPARA genes which play significant roles in high-altitude adaptation.

GENOMIC ADAPTATIONS OF YAKS TO HIGH-ALTITUDE ENVIRONMENTS

Since the advent of next-generation sequencing, numerous whole-genome sequencing studies of Tibetan mammals have been conducted to investigate the molecular mechanisms underlying high-altitude adaptation (Kang *et al*., 2022; Gao *et al*., 2022; Lan *et al*., 2021; Yue *et al*., 2022). The yak, being an ancient species exclusive to the Tibetan Plateau in China, has undergone extensive adaptation to challenging natural conditions, including hypoxia and low temperatures. Over the course of long-term adaptation, many genes have exhibited specific increases in transcriptional activities, regulating a range of metabolic activities within the body (Ge *et al*., 2021b; Yan *et al*., 2023; Terefe *et al*., 2022; Chen *et al*., 2023). Gene expression profiles reveal the activation of specific molecular pathways regulating responses to external stimuli and provide insights into the role of regulatory variation in adaptive evolution (Somero, 2005; Liu *et al*., 2021; Qi *et al*., 2018). Recent studies have identified key genes and pathways involved in various biological processes, including hypoxia adaptation. Hypoxia-induced changes in gene expression are coordinated by hypoxia-inducible factors (HIFs), which are fundamental transcriptional activators responding to reduced oxygen availability (Lisy and Peet, 2008; Webb *et al*., 2009). Among HIFs, HIF-1α and HIF-2α play pivotal roles in cellular adaptation to hypoxia, regulating multiple genes associated with energy metabolism, angiogenesis, erythropoiesis, iron homeostasis, and apoptosis (Schofield and Ratcliffe, 2004; Maxwell, 2005). Yaks, renowned for their adaptation to high-altitude environments and exceptional physical endurance, serve as a valuable model for understanding high-altitude adaptation at the molecular level. Sequencing of yak HIF-1α cDNA by Dolt *et al*. (2007) revealed variant-specific expression in the blood and liver, with no expression observed in the lung, heart, and kidney. Tissue-specific expression patterns may result from alternative splicing, as observed in plateau pikas, another high-altitude-adapted species (Zhao *et al*., 2004).

Comparing tissue-specific expression between yaks and cattle, it was found that HIF-1α exhibited ubiquitous expression in various tissues of yaks (kidney, heart, lung, spleen, and liver) as well as in blood, while HIF-2α expression was limited to endothelial cells. Expression levels of both HIF-1α and HIF-2α were higher in yak tissues compared to cattle. Transcriptome studies further revealed significant differences in gene expression patterns in the heart, lung, and gluteal tissue between the two species (Wang *et al*., 2015; Xin *et al*., 2019).

CONCLUSIONS

High-altitude environments are known for their harsh conditions, marked by low temperatures and oxygen pressure. The native high-altitude yak has developed unique adaptations through long-term selection, involving changes in morphology, physiology, biochemistry, and genetics. To comprehensively understand these adaptations, there is a need to expand studies and integrate research on DNA sequence polymorphism with analyses of transcriptional variation. Despite the synergistic impact of cold and hypoxia on performance at high altitudes, research has predominantly focused on hypoxia alone. The paragraph advocates for prioritizing joint investigations into these simultaneous environmental stressors. Additionally, it highlights the impact of climate change on yak habitats, emphasizing the necessity of further research to understand how these shifts contribute to changes in yak production and the livelihoods of highland communities.

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Data availability statement

All the data used in current article are available in the submitted version of article.

Statement of conflict of interest

The authors have declared no conflict of interest.

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