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REVIEW

The hypoxia adaptation of small mammals to plateau and underground burrow conditions

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Abstract

Oxygen is one of the important substances for the survival of most life systems on the earth, and plateau and underground burrow systems are two typical hypoxic environments. Small mammals living in hypoxic environments have evolved different adaptation strategies, which include increased oxygen delivery, metabolic regulation of physiological responses and other physiological responses that change tissue oxygen utilization. Multi-omics predictions have also shown that these animals have evolved different adaptations to extreme environments. In particular, vascular endothelial growth factor (VEGF) and erythropoietin (EPO), which have specific functions in the control of O_2 delivery, have evolved adaptively in small mammals in hypoxic environments. Naked mole-rats and blind mole-rats are typical hypoxic model animals as they have some resistance to cancer. This review primarily summarizes the main living environment of hypoxia tolerant small mammals, as well as the changes of phenotype, physiochemical characteristics and gene expression mode of their long-term living in hypoxia environment.

KEYWORDS

hypoxia adaptation, multi-omics, plateau, small mammals, underground burrow systems

1 | INTRODUCTION

Oxygen is a key factor in the growth, reproduction and metabolism of aerobic organisms[1] and oxygen content varies due to environmental factors, such as temperature, humidity, atmospheric pressure and altitude.[2] O_2 deficiencies may occur in environments of land-living animals such as high altitudes[3] and underground caves.[4]

Although mammals are largely intolerant of hypoxia, there are a few rodent species that live in hypoxic niches. These animals have evolved complex physiological and molecular adaptive systems that enable them to survive in hypoxic environments.[5] Low O_2 can lead to an increase in the production of reactive oxygen species (ROS) in the organism,[6] which in turn triggers oxidative stress.[7,8] However, antioxidant defense systems in organisms can counteract the adverse effects of ROS.[9] Maintaining a balance between energy production and consumption is also key to tolerating hypoxia.[10,11] In general, in order to adapt to hypoxia, animals can produce energy through anaerobic metabolism to maintain their metabolism,[12] and when the O_2 supply is limited, the metabolic rate of most hypoxia-tolerant animals shows a strong decline.[5,13] In hypoxia-tolerant newborn mammals, oxygen consumption ($\dot{V}O_2$) was shown not to exceed the baseline level during reoxygenation after hypoxia (15% O_2), and rapidly returned to the pre-hypoxia level, and lactate accumulation was observed only in more severe hypoxia (10% O_2).[14]

The organism responds to hypoxic stress by regulating downstream gene expression primarily through hypoxia inducible factor-1 (HIF-1).[15] HIF-1 is a heterodimeric transcription factor consisting of two subunits, HIF-1α and HIF-1β, of which HIF-1α is the active subunit.[16] In hypoxia, HIF-1α is stably transferred to the nucleus and forms a heterodimeric complex with HIF-1β, which regulates the transcription of >150 target genes.[17,18] These include the expression of two specific functional genes: vascular endothelial growth factor (VEGF) and erythropoietin (EPO).[19,20] VEGF increases endothelial cell proliferation, survival and migration, promotes angiogenesis, and delivers O_2 and nutrients[21,22]; EPO stimulates the proliferation and survival of red blood cell progenitors, which maintain the O_2-carrying capacity of the blood.[23] An inadequate hypoxic response is often associated with cardiovascular disease, cancer and COVID-19.[24,25] This review discusses the possible evolutionary mechanisms of hypoxia adaptation in small mammals living in long-term hypoxic environments and the evidence related to their possible functional role in the treatment of hypoxia-related diseases.

2 | HYPOXIC ENVIRONMENTS ON LAND

O_2 is essential for most aerobic organisms, and its reduction can produce significant physiological stress. At present, some hypoxia-tolerant small mammals have evolved effective strategies to survive under hypoxic conditions which may be related to their long-term existence in hypoxic environments such as the extensively studied plateau areas[26] and underground caves.[3]

2.1 | Plateau environments

Plateaus are special geographical areas of high lands that form unique natural landscapes and ecosystems.[27] China's plateau area is large and rich in natural resources. The area above 3000 m above sea level accounts for about one-sixth of the total area of the country and includes Tibet, Qinghai, Xinjiang, Yunnan and other provinces. The Qinghai-Tibet Plateau in particular is a large area known as 'the roof of the world' and contains Mount Everest.[28] Low temperatures, lack of O_2, strong ultraviolet light and dryness are distinctive features of the climate of the plateau.[29] These climate factors all directly or indirectly affect the survival of organisms. Typical atmospheric O_2, N_2 and CO_2 levels are approximately 21%, 78% and 0.03% respectively. However, the concentration of O_2 in the terrestrial environment can be altered by altitude and air circulation problems.[30] The atmospheric pressure and O_2 partial pressure decrease by about 0.67 and 0.14 kPa for every 100 m above sea level.[31] For example, the O_2 concentration at 4000 m above sea level is only 182.10 g/m^3, equivalent to 60.84% of sea level[30]; the absolute O_2 level at the summit of Mount Everest, at an altitude of 8844 m, is less than 1/4 of that at sea level.[32]

2.2 | Underground burrow systems

Globally, more than 300 mammals, such as blind mole rats (BMRs, *Spalax galili*),[33] naked mole rats (NMRs, *Heterocephalus glaber*),[34] plateau zokors (*Myospalax baileyi*)[35] and others, have settled in underground niches.[36] The absolute and relative amounts of O_2 in subterranean caverns fluctuate widely in both time and space.[37,38] For example, summer rainfall and winter frozen soil tend to create transient or prolonged low-O_2 conditions in the cave channels.[2,39-41] Spatially, the cave system can be a very complex structure.[37,38,41] For example, many colony-dwelling moles have deeper nests, an environment that can severely limit ventilation.[42] In addition, the presence of a large number of mammals may also lead to rapid and dramatic changes in gas composition of subterranean tunnels.[43] Despite the advantages of subterranean tunnels such as microclimatic stability, relatively low temporal variability in the availability of food resources and low predation risk, this is still a highly stressful environment.[42]

3 | HYPOXIC ADAPTATION STRATEGIES OF SMALL MAMMALS

O_2 is essential for the survival of organisms and is a key factor in maintaining normal life activities.[44] However, hypoxia may affect the normal metabolic activities and physiological functions of tissues, and even the vital status of the organism.[45]

3.1 | Physiochemical properties related to adaptation to hypoxic environments

It is possible that the morphology, blood properties, physiology, biochemistry and gene product structure and function of small mammals living on plateaus or in underground caves may have changed as they adapted to life in a low oxygen environment.[46-54] For example, some subterranean mammals that live for long periods of time in anoxic and dark caves have specialized sensory systems, such as specialized circadian rhythms,[55-57] heightened hearing,[58-60] degraded vision,[55,59,61-63] and oxyosphresia[64] (Table 1).

In addition to the possible evolutionary strategies of hypoxia adaptation that are seen in the species shown in Table 1, African mole-rats living in subterranean burrows have developed mechanisms to adapt to hypoxic, hypercapnic and hyperammonic tunneling systems.[65,66] They are able to tolerate extremely low oxygen tensions for several hours without any significant cellular damage.[67,68] North American deer mice (*Peromyscus maniculatus*), which live in the colder alpine regions, have alsobevolved more oxidative muscles that can maintain high rates of lipid oxidation to support thermogenesis.[69]

TABLE 1 Evolution of hypoxic adaptations in hypoxic-tolerant small mammals

Species	Significant physiological adaptations to hypoxic stress
Plateau pikas[a]	(1) Low-O_2 consumption and high-O_2 carrying capacity without excessive blood viscosity[147,148]; (2) Hb, RBC and HCT are not sensitive to altitude[149]; (3) Lower pulmonary artery pressure with hypoxia[150]; (4) High mitochondrial content in skeletal muscle and cardiac muscle[150]; (5) High density of tissue microvasculature[151]
Root voles[a]	High tissue-specific expression of HIF-1α and HIF-2α[152]
Qinghai voles[a]	(1) Increases hemoglobin synthesis to facilitate O_2 transport[94]; (2) Multiple genes (*Acs16*, *Gpat4* and *Ndufb7*, etc) are involved in the regulation of lipid synthesis, fatty acid β-oxidation, hemoglobin synthesis and electron linkage transfer[94]
Naked mole rats[b]	(1) Lower overall O_2 demand,[102] hemoglobin with a higher O_2 binding affinity[153]; (2) High ROS removal capacity,[78] hypothermia,[154] lower metabolic rate[155] and reduced heart rate[34,156] in the presence of hypoxic stress; (3) Substitution of residues 87 and 89 of HBA-T1 close to proximal histidine[157]
Mandarin voles[b]	(1) Eye degeneration[55]; (2) Higher capillary density and blood parameters (hematocrit, mean red blood cell volume, mean red blood cell hemoglobin)[39]; (3) High O_2 carrying capacity and low-O_2 consumption[1]; DNA repair enhancement, damage prevention and perception enhancement[2]
Blind mole rats[b]	(1) Subcutaneous eyes cannot form images[61,62]; (2) Under hypoxic conditions, EPO and HIF-1α are overexpressed[37,118] and the lungs have a greater capacity for gas exchange and a higher number of red blood cells[52]; Further elevation of hemoglobin oxygenase-1[25,79]; (3) High vascular density,[158] shorter O_2 diffusion distances[37,133,158]; (4) HBA-T1 AA substituents are located in the proximal binding site[159]; (5) Different methylation modifications of p53 can block transcriptional repressors[160-163]
Plateau zokors[c]	(1) Increased myocardial mitochondrial surface density, microvessel density and myoglobin content[164]; (2) Increased skeletal muscle microvascular density, myoglobin content and mitochondrial number and area[165]; (3) High O_2 partial pressure and O_2 saturation of arterial blood, with high O_2 utilization[166]; (4) Intramuscular lipid-soluble components, and alcohol-soluble components all have anti-hypoxic effects[166]

[a]High altitude.

[b]Subterranean.

[c]High altitude subterranean.

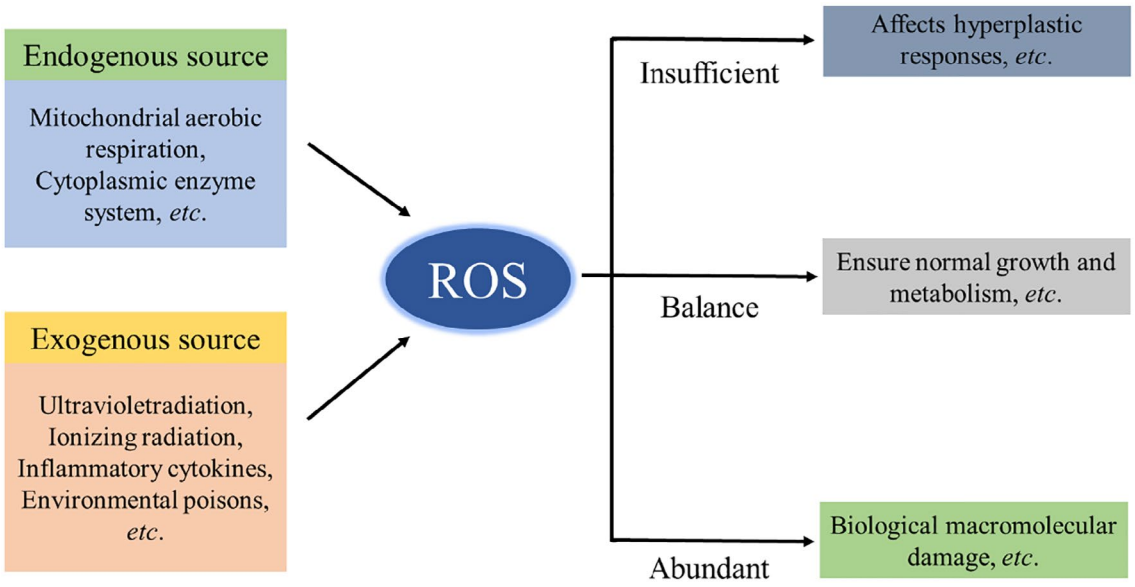

FIGURE 1 The effect of ROS content in the organism

3.2 | Antioxidant defense

The antioxidant defense system mainly consists of an antioxidant enzyme system and a small molecule antioxidant system.[70] The antioxidant enzyme system is mainly composed of enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx).[71] Under normal physiological conditions, ROS is a natural by-product of metabolism, and its production and clearance are in physiological equilibrium.[72] Too much or too little ROS can cause damage to the organism[72,73] (Figure 1). Hypoxia can lead to

increased ROS production *in vivo*,[6] which in turn triggers oxidative stress.[7,74] However, the antioxidant defense system in the organism can counteract the adverse effects of ROS.[9] ROS are also essential signaling molecules for cell growth, so the scavenging of ROS does not completely eliminate them, but maintains them at a low equilibrium to prevent disruption of the redox dynamic balance.

Many studies have indicated that mammals living in chronic hypoxic environments have adaptive tolerance to hypoxic stress.[74,75] For example, the antioxidant defense system of the Gansu zokors (*Myospalax cansus*) has evolved as a response to hypoxia, with the activities and gene expression of SOD and CAT being elevated in the brain and liver after hypoxia treatment compared to normoxia.[76] Previous studies have also found that some hypoxia-tolerant species can survive reoxygenation-induced oxidative stress cycles and maintain oxidative damage at manageable levels.[77] For instance, higher ROS scavenging capacity in NMRs may reduce oxidative damage associated with hypoxia/reoxygenation exposure (eg associated ischemia-reperfusion injury).[78] However, blind mole rats (BMRs) have been shown to have higher levels of ROS-processing enzymes compared to hypoxia-tolerant mammals.[79] One of a number of key transcription factors in BMRs, Nrf2, is essential for defense against oxidative stress and has a unique structure. Although Nrf2 is highly conserved in most mammals,[79] it carries 27 specific amino acid substitutions in BMRs, and six of them are within the Neh6 structural domain, and are essential for stabilizing the protein and its transcriptional activity under environmental oxidative stress.[80] The powerful antioxidant mechanism of NMRs is able to quench ROS before it damages DNA and other macromolecules, thus providing cellular homeostasis.[74,75] Another six species of African mole also showed no signs of protein or DNA damage during hypoxia and no change in the antioxidant capacity of the brain.[66,81,82] It may be that the brains of these species increase or maintain high levels of gene/protein expression and enzymatic activity of antioxidant enzymes other than GPx under hypoxic conditions, while helps them to cope with episodic oxidative stress.[79,83]

3.3 | Energy metabolism under hypoxic stress

In order to survive better in low-O_2 environments, O_2 'adaptors' either increase O_2 utilization or decrease metabolic rates at the whole body and cellular level.[84,85] In hypoxic environments, the body obtains energy through anaerobic glycolysis, and only 2 molecules of ATP can be produced from 1 molecule of glucose by anaerobic glycolysis.[86-89] Hence, the key for tolerating chronic hypoxia is to match metabolic demand with energy supply,[90-92] and most hypoxia-tolerant animals exhibit a strong decrease in metabolic rate during O_2 deprivation.[5,13]

The physiological responses to low-pressure hypoxia in small mammals at high altitude are diverse and numerous.[93] One study found that when Qinghai voles (*Neodon fuscus*) were exposed to a hypoxic environment, they appeared to improve fatty acid oxidation based on enhanced oxidative phosphorylation.[94] While up-regulation of Acot4 expression in the peroxisome of Qinghai voles helps them avoid excessive lipid depletion and deleterious effects on the plasma membrane.[94] In contrast, down-regulation of Gpat4 may reduce the synthesis of lysophosphatidic acid based on glycerol 3-phosphoglycerate and acyl-coenzyme A (acyl-CoA), thereby reducing the synthesis of phospholipid and triglyceride.[95,96] Down-regulated Gpat4 may also promote more acyl-CoA entering mitochondria for β-oxidation.[97] These adaptations may account for the maintenance of adequate energy supply to skeletal muscle tissue in Qinghai voles under hypoxic stress.[94] In addition, the expression of lactate-dehydrogenase-C in the skeletal muscle of plateau pikas (*Ochotona curzoniae*) increases their anaerobic glycolytic capacity, reduces the animals' dependence on O_2,[98] and enhances their adaptation to the hypoxic environment of the plateau.[99]

One of the biggest challenges faced by mammals in underground tunnels is the high energy cost of excavation in order to find limited food resources underground and maintain cave structures.[100,101] For example, NMRs, as is typical of the hypoxia-tolerant subterranean rats, have a basal metabolic rate that is about 30% lower than that of similarly sized mammals.[102] NMRs show different behaviors from other adult mammals, mainly consuming lipids under normoxia and undergoing anaerobic fructose-fueled metabolism during severe hypoxia, while their dependence on carbohydrate metabolism is increased by the depletion of hepatic glycogen and the increase in blood glucose during hypoxia.[34] Fructose-driven glycolytic respiration in the tissues of this species avoids feedback inhibition of glycolysis via phosphofructokinase, thereby supporting survival in hypoxic environments.[103] Gansu zokors also use fructose to accelerate energy supply based on glucose as the main metabolic substrate.[104]

3.4 | Key genes under hypoxic stress

Higher organisms have evolved complex regulatory mechanisms to respond to changes in O_2 concentration in the environment, and this key mechanism of adaptive change is closely connected to the hypoxia inducible activation pathway of hypoxia inducible factor-1α (HIF-1α).[104-106] To date, a number of key genes and proteins associated with hypoxia adaptation in small mammals have been published (http://ihypoxia.omicsbio.info/).

As a major regulator of the hypoxic response,[107] HIF-1α can target and regulate hundreds of genes directly or indirectly.[108] HIF-1α degrades rapidly under normoxic condition.[109] But in low-O_2 conditions, HIF-1α is responsible not only for the switch from oxidative phosphorylation to glycolysis, but also for other adaptive processes such as angiogenesis, cell survival and proliferation.[108,110,111] Interestingly, the expression level of HIF-1a mRNA in subterranean rats is significantly higher than that in ground mammals at all developmental stages.[38]

3.4.1 | Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a multifunctional growth factor that promotes angiogenesis and diastole, increases

vascular permeability, and promotes cell proliferation and survival.[112] Hypoxia can rapidly and strongly induce the mRNA expression of VEGF by increasing the stability and DNA ligation capacity of HIF-1α protein.[113] Research has found that tight control of angiogenesis may be a new mechanism for hypoxia tolerance in animals surviving in hypoxic environments.[25] For example, VEGF gene expression was significantly upregulated in the brains of BMRs under hypoxic conditions[114]; The mRNA expression of the VEGF gene in brain tissue and skeletal muscle of plateau zokors was significantly higher than that in Sprague-Dawley (SD) rats[111,115]; VEGF was also upregulated in brain tissue of Mandarin voles (*Lasiopodomys mandarinus*).[1,4] These studies provide further evidence that hypoxia-tolerant species may have a more effective angiogenic or neuroprotective mechanism for adapting to extreme subsurface hypoxic environments.

3.4.2 | Erythropoietin

Erythropoietin (EPO) is a hematopoietic cytokine that regulates erythropoiesis and promotes the differentiation and proliferation of relatively mature erythroid progenitor cells.[116] Moreover, EPO also has a strong pro-endothelial expression effect on vascular endothelial cells.[37] Hypoxia is the most important inducer of EPO,[37] and EPO expression in the kidneys of adult BMRs was significantly higher than in *Rattus norvegicus* under hypoxic stress.[37,117] The BMRs can also cope with the extreme hypoxic conditions of underground burrows during floods by overexpressing EPO *in vivo*.[118] The relative EPO mRNA expression in liver and kidney of plateau zokors at different altitudes increased with altitude, and the increase in kidney was five times greater than that in liver.[35,119] These findings provide important information for understanding the possible role of EPO in hypoxia-tolerant small mammals.

3.5 | Multi-omics studies on hypoxic adaptation in small mammals

With the rapid development of high-throughput sequencing, more and more data about the animal transcriptome or whole genome has been reported, and the discovery of large amounts of sequence information will provide useful reference data for animal evolutionary studies. Advances in high-throughput sequencing technologies have led to a number of studies using multi-omics approaches to analyze the adaptive evolution of extreme environments.[120-122]

Genome-wide data analysis has provided insights into the evolution of genome-wide adaptations to subsurface stress in subterranean mammals, in particular to the characterization of hypoxic adaptation, immune facilitation and sensory specialization responses to hypoxia-tolerant life.[43] Genomic studies have revealed adaptive evolution of genes related to vision (*Crygs*, *Crybb3*, *Gnat2*, etc) and skin (*Krt9*, *Pomp*, *Col4a4*, etc) in subterranean mammals and of the subterranean stress resistance complex (shelterin complex, proteasome complex, ribonucleoprotein complex, etc) in BMRs.[33,123,124] Large-scale transcriptome sequencing studies in BMRs show that apoptosis is inhibited and angiogenic factor expression is tightly regulated in hypoxic environments.[25,125]

Comparative transcriptomics was used for the first time to explore the skeletal muscle tissue responses to hypoxic conditions in Qinghai voles, Brandt's voles and Kunming mice, and it was found that these species use different strategies of O_2 transport and energy metabolism to cope with hypoxic conditions.[94] Among them, Qinghai voles promotes oxygen transport by increasing hemoglobin synthesis. This species also regulates lipid synthesis, fatty acid β-oxidation, hemoglobin synthesis, electron-linked transmission, and other biological processes through a combination of genes, including *Acs16*, *Gpat4*, and *Ndufb7*, and thereby ensures that the energy supply to skeletal muscle tissue remains sufficient under low-oxygen conditions.[94] Analysis of transcriptomic data from plateau zokors and NMRs focusing on amino acid loci and gene expression levels revealed the important adaptive evolution in the expression of amino acid sites and genes related to O_2 transport, O_2 metabolism, DNA repair and other hypoxia-adapted proteins in these two subterranean rats.[126] Transcriptome analysis of the brain and muscle in BMRs also found significant overexpression of genes associated with anti-apoptotic, cancer, embryonic development and angiogenesis processes.[25] These mechanisms help BMRs to survive in subterranean low-O_2 environments. In addition, analysis of the brain transcriptome of Mandarin voles under hypoxic conditions also indicated that the upregulated pathways were mainly those that inhibited angiogenesis and responses to external stimuli, while the downregulated pathways were related to O_2 consumption processes such as oxidative phosphorylation and protein secretion, suggesting that Mandarin voles have a greater ability to sense and regulate O_2.[2]

4 | ANTI-TUMOR MECHANISMS OF SUBTERRANEAN MAMMALS

For many mammals, tumors are a major source of death in later life.[127] Despite the importance of laboratory mice in understanding the mechanisms of carcinogenesis, this model organism for cancer susceptibility has failed to provide satisfactory information about human cancer prevention mechanisms and treatment strategies (http://www.safermedicines.org/quotes/cancer.shtm)149. Therefore, it would be extremely useful to study animals with natural anti-cancer abilities as models to find ways to prevent cancer before it occurs. Numerous studies have found that subterranean mammals such as NMRs and BMRs have anti-cancer abilities.[128] Further research on these mammals may benefit human health if these mechanisms can be activated in human cells.

4.1 | Blind mole rats

Due to their long-term subterranean habitat, the BMRs are well adapted to anoxic conditions,[53] which makes them a hypoxia-tolerant

model organism.[74] Spontaneous cancer has never been observed in BMRs.[129] The anti-cancer effects of BMRs mainly derive from the following adaptations: (1) Expression of p53 target genes in hypoxia-tolerant subterranean moles is hypoxia dependent and resembles the expression pattern in solid tumors.[130] Cloning of p53 from BMRs reveals exchange of arginine (R) for lysine (K) at codons corresponding to positions 174 and 209 in human for the p53 DNA binding domain. These two amino acid changes are identical to known human tumor-related mutations.[131,132] (2) A unique acetyl heparinase splice variant significantly reduces tumor size and metastatic activity.[75] (3) BMRs have an efficient DNA repair capability and editing mechanism.[33,133,134] (4) Compared to mice, BMRs have a more active innate immune system and elevated expression of tumor suppressor genes associated with the extracellular matrix.[129] (5) Normal BMR fibroblasts can inhibit growth and kill cancer cells either through direct interaction with cancer cells or through soluble factors.[128] (6) The somatostatin receptor-4 is more highly expressed in BMR tissue[129] and can inhibit the proliferation of normal or tumor cells.[135] These factors may also be the adaptive mechanism of BMRs resist cancer development.

4.2 | Naked mole rats

NMRs are remarkable for their longevity and almost complete resistance to cancer.[60,136] Hyaluronan and a new glycosaminoglycan variant have been identified as key substances in the anticancer mechanism of naked mole rats.[137,138] The glycosaminoglycan substance is a high molecular weight hyaluronan (HMW-HA), which is 5 times larger than the corresponding variant in mice and humans.[139] HMW-HA accumulates in large quantities in naked mole rat tissues due to the reduced activity of hyaluronan degrading enzymes and a unique sequence of hyaluronan synthase 2.[139] In addition, 4422 high quality lncRNAs have been successfully identified in the NMR genome. The functions of lncRNAs in NMRs were predicted by co-expression analysis. It was found that about 61.93% of lncRNAs in NMRs were highly correlated with the expression of oncogenes.[140,141] Moreover, the lncRNAs in NMRs may provide a natural anti-cancer mechanism by regulating the production of hyaluronan.[141] Although NMRs have a higher mutation rate than mice, they are less likely to develop tumors because they are less prone to inflammatory responses.[142,143] As a tumor suppressor activated by carcinogenic stress, ARF is a tumor suppressor gene in NMR, but it is inhibited in most mammals.[144,145]

5 | CONCLUSION AND PROSPECTS

China has the highest altitude plateau in the world and rich animal resources. Thus, it is an ideal area to study the adaptive evolution of hypoxic species at different altitudes. A large number of studies have been carried out using modern molecular biology methods to investigate the physiological and biochemical characteristics and molecular mechanisms of hypoxic adaptation in highland species, and breakthroughs have been made. These will provide important guidelines for the control of highland diseases in human and livestock. In addition, mammals living in subterranean caves for long periods of time may have evolved hypoxic adaptations, and the genetic basis and molecular mechanisms of these species have also been obtained through systematic analysis. This research will help to advance our understanding of human hypoxia-like diseases, particularly COVID-19 (a new highly infectious disease caused by Severe Acute Respiratory Syndrome coronavirus infection,which can cause severe hypoxia in the body[24,146]). Interestingly, it has been found that naked mole rats and blind mole rats, typical hypoxic model animals, are not only well adapted to the hypoxic environment, but also have the ability to resist tumors.[128] Their anti-tumor mechanisms make these animals ideal model species for human cancer research.

However, the mechanisms of hypoxia adaptation in hypoxia-tolerant mammals are not yet sufficiently well studied. For example, the correlation analysis between the phenotypic, physiological and biochemical characteristics of these mammals and their gene evolution and expression are not perfect, and further discovery and validation of signaling pathways related to hypoxia adaptation is urgently needed. Studying the molecular mechanisms of adaptation in hypoxia-tolerant animals is indeed one of the topical issues in biology and medical research. Continuing investigation of the mechanisms of hypoxia adaptation in hypoxia-tolerant mammals through a combination of whole genome sequencing, transcriptome sequencing, single-cells sequencing and epigenetics may provide a suitable experimental animal model for the study of human hypoxic diseases.

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CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest to this work.

AUTHOR CONTRIBUTIONS

MKL conceived and wrote the original draft of the manuscript. ZLW, HC and TS revised the manuscript. All authors critically read and contributed to the manuscript, approving its final version.

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