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REVIEW

Adaptation of mammals to hypoxia

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Abstract

Oxygen plays a pivotal role in the metabolism and activities of mammals. However, oxygen is restricted in some environments—subterranean burrow systems or habitats at high altitude or deep in the ocean—and this could exert hypoxic stresses such as oxidative damage on organisms living in these environments. In order to cope with these stresses, organisms have evolved specific strategies to adapt to hypoxia, including changes in physiology, gene expression regulation, and genetic mutations. Here, we review how mammals have adapted to the three high-altitude plateaus of the world, the limited oxygen dissolved in deep water habitats, and underground tunnels, with the aim of better understanding the adaptation of mammals to hypoxia.

KEYWORDS
hemoglobin, high-altitude, hypoxia, marine mammals, subterranean mammals

1 | INTRODUCTION

The delivery and utilization of O_2 is of great importance to the survival of many organisms. In eukaryotic organisms, O_2 oxidizes glucose to carbon dioxide and water, and generates adenosine 5′-triphosphate (ATP), which is essential for their survival and activities.[1] However, in some situations such as high-altitude and deep ocean habitats, subterranean tunnels, and outer space, oxygen is limited. These hypoxic environments could limit physiological functional capacity, reproductive health and even survival,[2] for example when superoxide anions are generated when electrons escape from the respiratory chain and combine with O_2, or when organisms suffer from hypoxia, which can lead to damage in the brain,[3] lung,[4] retina,[5] liver,[6] and kidney.[7]

Hypoxia occurs in a variety of situations including at high altitude, deep in the ocean, in subterranean tunnels, and in concentrated populations, or when breathing mixtures of contaminated gases. Such conditions cause various diseases or even death of the organism. In order to cope with such stresses, organisms have evolved strategies such as unique circulatory, respiratory and hematological adaptations, including single nucleotide variations (SNV), copy number variations (CNV), transposable elements, differentiated gene expression, isoforms and methylations. Many genes,[8] regulators and mutations have been identified as candidates for hypoxia adaptation using whole genome data.

2 | ADAPTATION TO HIGH-ALTITUDE PLATEAUS

There are three main plateaus across the world—the Tibetan Plateau, the Andean Plateau, and the Ethiopian highlands. As barometric pressure is lower at high altitude, the atmospheric pressure of oxygen is therefore lower for all the resident organisms living at high altitude (the oxygen pressure in the atmosphere on the high-altitude plateaus is ~40% lower than the sea level).[9] This decreased oxygen availability could impair the metabolism and physical performance of resident

organisms, threatening their health and survival.[10] As a result of long-term adaptation and evolution, these organisms have adapted to their local hypoxic environments in different ways. Both plastic and evolved variations in respiratory, cardiovascular and metabolic traits can contribute to high-altitude adaptation. Ethiopian, Andean and Tibetan populations are reported to have evolved different strategies to adapt to lower barometric pressures.[2] One example is that hemoglobin concentrations and oxygen saturation are different between animals from the three plateaus. Hemoglobin is essential for oxygen transportation, taking oxygen from respiratory organs to tissues where metabolism is conducted. Thus hemoglobin concentration and oxygen affinity are considered important in high-altitude adaptation. In organisms living on the Tibetan plateau, hemoglobin concentration is independent of altitude, while in contrast, it rises with altitude in organisms living on the Andean highland.[11] In the Ethiopian highlands, both hemoglobin concentration and arterial oxygen saturation are independent of altitude.[12,13] Oxygen saturation is lower but resting ventilation is higher in Tibetan populations than those in Andes,[11] and the hypoxic pulmonary vasoconstrictor response is lower in highlanders than in acclimatized lowlanders.[14] Compared to Han Chinese, Japanese Europeans and Africans, the Tibetans have a specific haplotype in *EGLN1*, which was proved to have a significant association with hemoglobin concentrations, suggesting a causal mutation contributing to high-altitude adaptation. Under hypoxic conditions, EGLN protein is inhibited, and this protein negatively regulates HIF protein (Figure 1: figure S1 from Xiang (2013)[15]). The genetic diversity of the two amino acid positions of D4E/C127S in Tibetan EGLN1 protein is present under hypoxic conditions (1% O_2), and the level of *HIF-2α* protein is lower than that of ordinary people. Under different oxygen concentrations, Tibetans and ordinary people also have significant differences in their responses to EPO-stimulated erythrocyte production (Figure 2: figure 3b from Xiang (2013)[15]). They have an innate advantage in EGLN1/HIF/EPO metabolic pathways that allows them detect oxygen levels and regulate hematopoietic function. This is why Tibetans have an advantage in survival under high altitude conditions.[15]

Besides hemoglobin concentration, oxygen affinity can also affect oxygen uptake and delivery. The affinity of oxygen for hemoglobin also plays a pivotal role in adaptation to hypoxia. Different globin haplotypes have been shown to have different oxygen affinities in deer mice, with β-globin being predominant at high altitude, because of its increased oxygen affinity.[16] Other organisms like bar-headed geese,[17] Andean geese,[18] and yaks[19] also display high hemoglobin-O_2 affinity. Oxygen delivery can also affect hypoxia adaptation. Although the hemoglobin concentration of organisms on the Tibetan plateau is independent of altitude, and their oxygen saturation is comparatively low, the speed of blood flow is faster, which also leads to high efficiency of O_2 delivery.[20]

In addition to physiological adaptations to hypoxia, genetic variations also adapt organisms to local environments. Comparative genomics have been conducted for organisms from the Tibetan,[21–25] Andean[21,26] and Ethiopian plateaus.[27,28] Many of the genes involved in the hypoxia-inducible factor (HIF) pathway have been identified

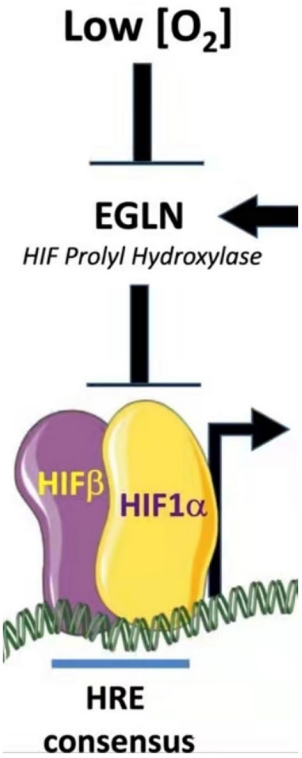

FIGURE 1 Partial mechanism diagram of EGLN gene regulation

as candidate adaptive elements from several species, including humans, mammals and birds. *EPAS1* (*endothelial PAS domain containing protein 1*), *PPARA*, and *EGLN1* (*egl-9 family hypoxia inducible factor*) are frequently reported in high altitude adaptations[8,9,23–25,29,30] in Tibetans, while in Ethiopians, *BHLHE4* is reported to be an important gene that adapts to hypoxia.[2] In the Andeans, *EGLN1* was also identified as a candidate adaptive gene with a strong signature for positive selection.[21] This suggests that organisms from the three high-altitude areas have adapted to hypoxia in different ways. It is reported that in yaks[31] and antelopes[32] genes from metabolic pathways are also involved in high altitude adaptation. Among Tibetan mastiffs, 12 genes have been proved to be beneficial for adaptation to the plateau environment, and *EPAS1*, *SIRT7*, *PLXNA4*, and *MAFG* were of great importance in adaptation to hypoxia.[33] The mastiffs were originally native to low altitude areas[34] but were intentionally selected for adaptation to a higher altitudes by selecting for thicker coats and lower hemoglobin levels. The Tibetan antelope, an animal that can run at 80 km per hour for several hours, the expression of CaMK II δ is increased, and the expression of ANP, a marker of myocardial hypertrophy, is up-regulated by the CaMK II δ pathway, while BNP, a marker of heart failure, is not significantly increased, suggesting that the increased expression of CaMK II δ gene may be related to myocardial hypertrophy and left ventricular systolic force under hypoxia stress. However, there is no significant increase in the level of the BNP gene, suggesting that the myocardial hypertrophy of Tibetan antelopes is a physiological adaptation to hypoxia resulting from long-term residence in a hypoxia environment, and is a compensatory response to increase myocardial contractility. This

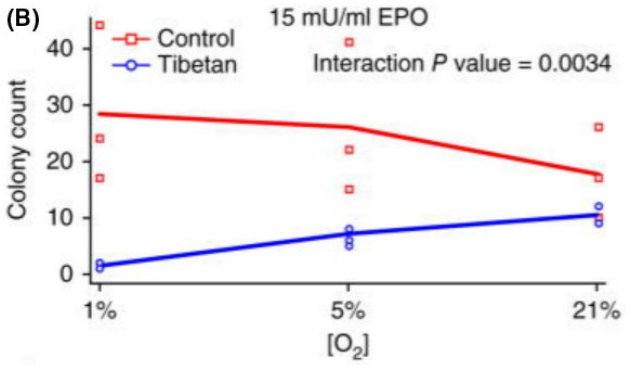

FIGURE 2 Response of Tibetan and lowland people to EPO-stimulated erythropoiesis under different oxygen concentrations

indicates that Tibetan antelopes are plateau-adapted animals that have acquired a genetic adaptation of their hearts to the low oxygen environment of the plateau after a long period of natural selection. Genes related to DNA repair, hypoxia adaptation, and ATPase production have evolved by positive selection.[32]

3 | HYPOXIA TOLERANCE IN SUBTERRANEAN MAMMALS

3.1 | The evolution of underground mammals

The evolution of subterranean mammals over more than 50 million years old in nature—an evolutionary experiment of mammals adapting to life underground—is a long-term research topic.[35] The adaptive

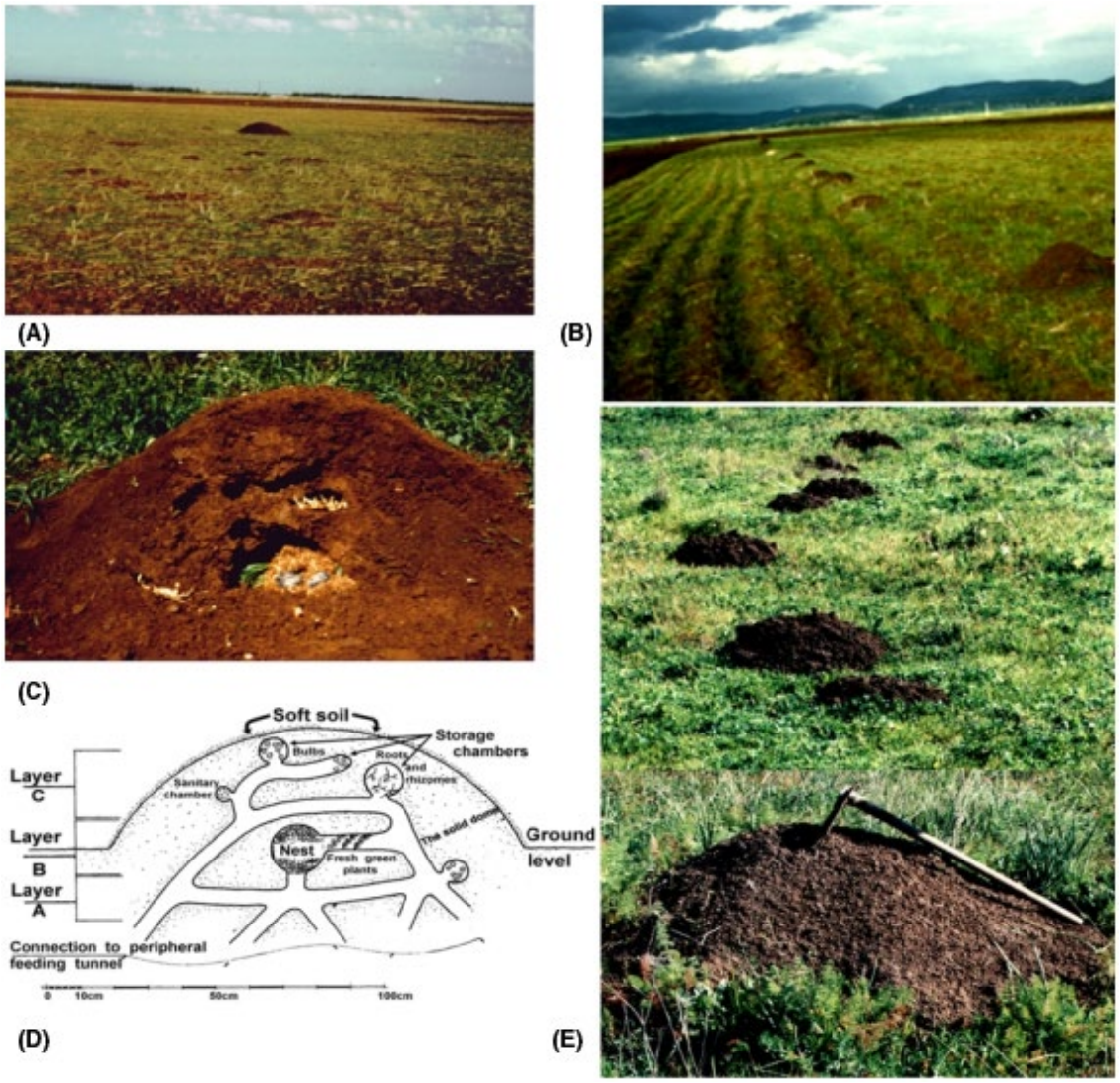

FIGURE 3 Underground tunnels of the subterranean mammal *Spalax*. (A, B) Mounds of *Spalax* in the field; (C) Inside the burrow system; (D) schematic of the burrow structure; (E) Mounds of *Spalax* for reproduction

convergent evolution of global subterranean mammals currently involves three orders: rodents, insectivores, and marsupials, including hundreds of species in 11 families and 50 genera. After the gradual climate cooling and drought in the transitional period between the middle Eocene and the early Oligocene, a global evolution process began to take place in earth's geology, climate and biota. During the Cenozoic period, the ecological threats to open wild biota included increasingly severe drought, a colder climate and terrestrial life. These climate changes created the conditions for the evolutionary process of neotertiary adaptive radiation of unrelated mammals on all continents to underground ecological areas (Figure 3: figure 2.1 from Nevo (1999)[35]).

3.2 | The subterranean ecotope

The subterranean ecotope[36] is structurally simple. It is a relatively stable microclimate, with a highly specialized and low-productivity sealing system.[37] In terms of physical (microclimate) and biological (food and low predation) elements, the underground environment is better buffered and more predictable than the ground environment, resulting in a narrow underground niche.

The microclimatic and low predation benefits are counterbalanced by multiple stresses. These include total darkness, hypoxia, hypercapnia, energetic cost, and much pathogenicity.[38] The following section will focus on hypoxia tolerance in the *Spalax ehrenbergi* superspecies in Israel.

3.3 | Spalacidae subterranean rodents globally and Israel

The Spalacidae are Eurasian, particularly east Mediterranean, rodents. They are highly adapted to life underground, genomically, morphologically, physiologically, and behaviorally.[35] Because large and complex breeding mounds were found in poorly drained clay soil in Israel, five species of the blind underground mole of *S. ehrenbergi* superspecies have been extensively and interdisciplinarily studied.[39] A list of studies by Nevo and colleagues appears at http://evolution@haifa.ac.il. The four chromosomal species *Spalax galili* (2n = 52), *Spalax golani* (2n = 54), *Spalax carmeli* (2n = 58), and *Spalax judaei* (2n = 60) form an adaptive evolutionary speciation trend associated with increasing climatic aridity southwards (2n = 52,54→58→60) and have been described interdisciplinarily.[40] The genomic adaptations to life underground of the four chromosomal species appear in Fang et al.[41] The genomic evolution of the five species appears in Li et al.[42] The fifth non-chromosomal species, speciated genically and sympatrically on chalk (progenitor) and abutting basalt (derivative), was named temporarily *S. galili* basalt. It has been described in several papers.[42–47]

3.4 | Hypoxia tolerance in *S. ehrenbergi* superspecies

The first field evidence of the blind subterranean mole rats of the *S. ehrenbergi* superspecies was the large, high breeding mounds built by the females after the first rains in October in clay soil with bad drainage.[39] Figure 3C illustrates how the females align the breeding mounds on small ridges above the ground; this was beautifully evident a few kilometers east of Acre in the early 1960s. In several cases we found wet females in the breeding mounds escaping from the flooded burrows below. Our first physiological tests highlighted a decrease from the humid north to the xeric south in hematocrit and hemoglobin concentrations in the four chromosomal species.[48] Likewise, adaptive heart and breathing phenotypes differentiating the chromosomal species declined in frequency moving southwards.[49]

Evidence for improved myocardial oxygen delivery and function during hypoxia has also been demonstrated.[50] Finally, hypoxic survival differs between two species, being higher in humid-environment *S. galili* (2n = 52) than in arid-environment *S. judaei* (2n = 60).[51] Increased blood vessel density allows *Spalax* to tolerate to underground hypoxia.[52] More and more evidence shows that there are structural and functional differences in genes related to hypoxic stress between the underground *Spalax* species and the above-ground rat (*Rattus norvegicus*), reflecting 47 million years of evolution of *Spalax* to fluctuating gas composition in underground habitats—molecular adaptation experienced as effective survival. However, as the arrangement of small breeding hills raised on the ground shows,[39] this is not the case for animals escaping upwards to a cave in a flooded Dobi. The soil moisture, oxygen (O_2) and carbon dioxide (CO_2) composition of the underground caves in the natural habitats of three Israeli underground zokors were studied. Based on comparison of soil types, two populations with relatively close geographical locations are mainly studied.[51] The *S. carmeli* breeding mound in northern Israel is located in a flooded area with very high water content and poorly drained soil with high viscosity.[53] The maximal CO_2 levels (6.1%) and minimal O_2 levels (7.2%) were recorded. During the observation period, the gas fluctuation levels in the habitats of the different *Spalax* species were relatively similar. There was a significant difference in gas concentrations between adjacent populations living in heavy soil or light soil rather than between the two species: compared with relatively light soil (terra rossa and rendzina), heavy soils (clay and basalt) have lower O_2 and higher CO_2. The gas composition and soil water content of adjacent sites with different soil types indicated that the hypoxia-hypercarbonic stress levels of different populations of the same species are quite different.

4 | MOLECULAR STUDIES OF HYPOXIA IN SPALAX SPECIES

Based on transcriptome results in *S. galili*,[54] a mass of splice variants, SNPs, and novel transcribed regions were identified. These results help to further identify genes and gene regions that evolved during adaptive radiation to a subterranean hypoxic niche of blind mole rats. Adaptive hypoxic tolerance in *Spalax* has been shown by adaptations in vascular endothelial growth factor.[55] A comparative study of the erythropoietin gene has been conducted in the four chromosomes of the *S. eherenbergi* superspecies,[53] as has ontogenetic

expression of erythropoietin and hypoxia inducible factor-alpha genes to hypoxia.[56] Blind subterranean mole rats of the *S. ehrenbergi* in Israel have evolved a variety of adaptive strategies to cope with subsurface hypoxia conditions. Hypoxia-inducible factor-1alpha (HIF-1alpha) and erythropoietin (*EPO*) are key factors for normal erythropoiesis and angiogenesis. We have proved using real-time polymerase chain reaction (PCR) that the expression level of EPO mRNA in the fetal liver and kidney of *Spalax* is higher than that of *Rattus* under normoxia and hypoxia, which enhances the fetus's underground red blood cell production and enables it to adapt to sudden and sharp fluctuations in oxygen supply in underground life. Adult *Rattus* kidney and liver, and adult *Spalax* liver express similar levels of EPO mRNA under normoxia and hypoxia. However, under normoxia and hypoxia, the expression levels of EPO mRNA in the kidney and liver of adult *Rattus* and the liver of *Spalax* were similar, while under hypoxic conditions, the EPO mRNA expression level in the adult *Spalax* kidney (the main site of erythropoietin production in adult mammals) is twice that of *Rattus*. *Spalax*'s hif-1α mRNA expression level at all developmental stages was significantly higher than that of *Rattus*, reaching a peak in neonates, showing an adaptation to hypoxia.[57]

Differential expression profiling of four chromosomal variants of the Israeli *S. ehrenbergi* superspecies, bioprospecting for hypoxia tolerance, has been studied genomically.[58] The blind subterranean mole rat of the *S. ehrenbergi* superspecies lives in an underground environment with fluctuating levels of oxygen and carbon dioxide, and is an excellent model of hypoxia tolerance. The unique structural and functional adaptations of the cardiovascular and respiratory systems enable it to survive under severely reduced oxygen tension. The study clarified that the natural variation and evolutionary changes of this superspecies under hypoxic conditions may have biomedical value in research into ischemic syndrome and cancer. In this study, we compared expression profiles of muscle tissue at normoxic (21%) and hypoxic (3%) levels of oxygen concentration between two allospecies of the *S. ehrenbergi* superspecies exhibiting differential hypoxia tolerance in accordance with their ecological regimes. Cross-species hybridization using a mouse cDNA array containing 15 000 genetic elements was analyzed. The results revealed that in response to hypoxic stress, many genes involved in the management of angiogenesis, apoptosis and oxidative stress have species specificity. Among the most striking results are differential expressions of cardiac ankyrin repeat protein (Carp), activating transcription factor 3 (Atf3), LIM and cysteine-rich domains 1 (Lmcd1), cysteine and glycine-rich protein 2 (Csrp2), and Ras homolog gene family, member B (RhoB). These findings support the hypothesis that allospecies of the *S. ehrenbergi* superspecies have different adaptations to fluctuating oxygen tension, which was also confirmed by Arieli and Nevo.[51] These differences may involve specific metabolic pathways and functional adaptations at the structural and molecular levels.

The tumor suppressor gene p53 controls tumor cells and inhibits tumors by regulating the transcription and synthesis of downstream genes. Due to insufficient blood supply, the local microenvironment in the tissues where tumors occur has low oxygen content. The p53 gene of tumor cells stimulated by hypoxia will undergo mutations. This mutation enhances the survival ability of cancer cells in a hypoxic environment. Furthermore, it controls the responses of cells to a variety of stress conditions, including DNA damage and hypoxia. p53 significantly inhibited the activity of the BNIP3 promoter and thus the transcription and translation of BNIP3 under both hypoxia and normoxia conditions. In-depth analysis has found that p53 can inhibit the transcription of BNIP3 by recruiting the repressor mSin3a to the p53 response element region on the BNIP3 promoter. In addition, p53 can protect cells from hypoxia-induced apoptosis by specifically inhibiting the expression of BNIP3.

Studies have shown that in the hypoxia-tolerant model organism *Spalax*, the DNA binding domain of p53 contains a specific Arg174Lys amino acid substitution.[59] This substitution reduces the effect of p53 on the transcription of apoptotic genes (apaf1, puma, pten and noxa), and enhances the effect on human cell cycle arrest and p53 stable/homeostasis genes (mdm2, pten, p21 and cycG). By cloning the promoter region of Spalax apaf1 and the intron region of mdm2, it was found that the two contained the same P53 response elements. The transcriptional activity of Spalax arg174lys mutant p53 on target genes of two species was also studied. Spalax mutant p53 lost the ability to induce apaf1 transcription, but showed increased induction of mdm2 transcription. These results led to the conclusion that Spalax has evolved a mechanism to adapt to hypoxia.

Neuroglobulin (Ngb) and cytoglobulin (Cygb) are respiratory proteins that bind to oxygen, and therefore may participate in the molecular adaptation to hypoxia of *Spalax*.[60] Ngb is mainly expressed in vertebrate nerves, while Cygb is distributed in the cytoplasm and nucleus of nerve cells in specific areas of the brain. The expression of the two is positively correlated with the increase of hypoxia tolerance. The former has the ability to store and transport oxygen and protect nerves, and the latter can increase the tolerance of brain tissue to hypoxia and resist damage caused by oxidative stress. The physiological functions of these two proteins are not fully understood. The coding sequences of Spalax Ngb and Cygb have strong conservation. Under normoxic conditions, Ngb mRNA and protein levels of *Spalax* are three times that of *Rattus norvegicus*. Hypoxia caused about a twofold down-regulation of Ngb mRNA in the brain tissues of rats and moles. In addition, parallel regulatory responses of myoglobin (Mb) were also found in *Spalax* and rat muscles, indicating that Mb and Ngb have similar functions. Although Cygb expression increased in *Spalax* and rat brain under normoxic conditions, it was not increased in the heart and liver, indicating its tissue specificity. Hypoxia induced Cygb transcription in the heart and liver of both mammals, with *Spalax* heart mRNA up-regulated the most (12-fold). Our data also show that tissue globin helps to significantly increase the tolerance of Spalax to environmental hypoxia. This is consistent with the cytoprotective effects of Ngb and Cygb under pathological hypoxic/ischemic conditions in mammals.

If the oxygen level is not sufficient to maintain cell energy production, this threatens the survival of mammals. The most

metabolically active tissues (such as nerve cells) are very sensitive to the reduction of oxygen (hypoxia). Humans are severely affected by diseases caused by hypoxia, such as stroke or myocardial ischemia. Therefore, studying the specific adaptability of mammals living in a natural hypoxic environment where low oxygen tension limits the availability of oxygen to organisms is highly relevant to efforts to prevent and treat hypoxic diseases.

5 | A COORDINATED NECROTIC CELL DEATH MECHANISM MEDIATES CANCER RESISTANCE IN BLIND MOLE RATS

The blind mole rat *Spalax* (BMR) is a common small underground rodent in the eastern Mediterranean. It is characterized by adaptation to underground life, longevity (the longest life span recorded is 21 years) and resistance to cancer. Spontaneous tumors have never been observed in *Spalax*. In order to understand the mechanism of this resistance, we tested the in vitro growth of fibroblasts from the southernmost species Jewish Spalax and the northernmost species *Gorani Spalax*. After *Spalax* cells began to secrete IFN-β, the cells proliferated 7–20 times actively, and a large area of necrotic cell death occurred within 3 days. However, the phenomenon of necrotic cell death had nothing to do with culture conditions or shortening of telomeres. The results of the study indicate that the cancer resistance of *Spalax* is mediated by the p53 and Rb pathways, and the release of IFN-β (interferon β) triggers a large-area necrotic reaction to excessive proliferation. We thus identified a unique mechanism that helps this mammal, which is well-adapted to living underground, resist cancer and is highly related to hypoxia tolerance.

6 | ADAPTATION TO HYPOXIA IN MARINE MAMMALS

The dissolved oxygen in water can fall below 2.0 mg/L, which leads to hypoxia and can be a permanent stress in marine organisms.[61] Therefore, marine mammals like whales and dolphins are exposed to hypoxia all their lives. Many species exhibit prolonged breath-holding capabilities, which allow the organisms to move into deep waters and remain submerged for extended periods.[62] After long-term evolution, these animals have evolved specialized physiology[62] and genetic mutations. Hindle has reviewed[62] the developments in physiology and genomics of marine mammals that evolved as adaptations to dive hypoxia; these include cardiovascular control, regional tissue blood flow being calibrated with metabolic need, and the ability to almost exhaust body oxygen store, which increased capacity to adapt to hypoxia.[63,64] In Minke whales, several genes were identified as facilitating the aquatic adaptation to hypoxia by comparative genome comparison. Species specific mutations were found to be related to resistance to reactive oxygen species, stress of hypoxia and high salt concentration,[65] suggesting adaptations for increased diving duration. Genomic analysis of the adaptive enrichment found that the polar bear's abdominal muscles had graphene oxide associated with heme binding, which may affect the oxygen storage and transport of heme protein. A previous deep dive physiology investigation of Weddell seals found that their spleen is very large. This contractible spleen is like an oxygen tank, capable of injecting oxygenated red blood cells into the blood circulation during prolonged diving.[62] The discovery of genes encoding respiratory pigments, endothelin pathway genes (EDN1, EDN2, EDN3, EDNRA and EDNRA), genes encoding antioxidants and cellular stress response components (OGT), and other gene variants point to high levels of antioxidants being involved in the adaptations to diving in various species. In a very recent study, 17 marine mammals, including 11 cetaceans and six pinnipeds, also showed putatively selected genes related to deep diving.[66] In conclusion, the marine mammals show different adaption strategies to hypoxia.

TABLE 1 Genes/pathways and regulators of hypoxia adaptation

Species	Genes/pathways and regulators
Tibetans	EPAS1, PPARA, EGLN1
Ethiopian	BHLHE4
Andeans	EGLN1
Tibetan mastiff	EPAS1, SIRT7, PLXNA4 and MAFG
Tibetan antelope	CaMK II δ, BNP
Spalax	EPO, hypoxia inducible factor-alpha, p53
Israeli Spalax ehrenbergi superspecies, *Spalax*	p53, Carp, Atf3, Lmcd1, Csrp2, RhoB
Marine mammals	genes encoding respiratory pigments, EDN1, EDN2, EDN3, EDNRA and EDNRA, OGT

7 | CONCLUSIONS AND PROSPECTS

Hypoxia is widespread in high altitude areas, subterranean burrow systems, deep ocean habitats and in space. As human activities expanded from the earth to the deep ocean and into space, adaptations to resist to hypoxia should be the subject of future studies. Although genes/pathways and regulators have been identified as candidates for hypoxic adaptation mechanisms (Table 1), physiological and functional experiments are required to test all the hypotheses. It is still open to question whether the genotype-phenotype relationship is cause and effect or just the association of effect and secondary consequences.[67] In order for human health to benefit from these analyses, the underlying mechanisms must be elaborated. As study techniques develop faster and faster, so human activities can expand into more challenging environments.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTION

Thanks to Eviatar Nevo for helping to organize the framework of the article, thanks to Zhenglei Qiao for helping to improve the summary and discussion section of the article, thanks to Qijiao Duan for helping to improve the chart section of the article.

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