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Genetic & Immunological Effects of High Altitude Illnesses on Human Health : A Review

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Hypobaric hypoxia environments present a major concern after ascending to high altitudes (2,500+ meters) because the immune system's inability to adapt to sudden changes in O_2 concentration quickly, causing tissue hypoxia if left untreated and leading to the development of high altitude illnesses (HAI). Acute altitude illnesses (AAS) and chronic altitude illnesses (CAI) are the two main types of HAI. AAS is subdivided into acute mountain sickness (AMS), chronic kidney disease (CKD), high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE), while CAI is subdivided into chronic mountain sickness (CMS) and high altitude pulmonary hypertension (HAPH). Given that over 140 million people live permanently at elevations of 2,500 meters or higher, and that 40 million people visit such locations on a seasonal basis, it's easy to see why studying the pathophysiology, mechanism, and treatment of such diseases has become critical. Although many genes are affected by high altitude hypoxia, the focus of this review was on the role of five specific genes and proteins (HIF-1, EPAS1/HIF-2, VEGF, P53, and VHL), whose expression is influenced by hypoxia and immunological changes in human response to immune-mediated inflammatory diseases (IMIDs), microbiota diversity in the gut, and physiological changes in the blood.

Keywords: high altitude illnesses; acute altitude illnesses; chronic altitude illnesses; immunological effect; genetic effects; hypoxia; microbiota; inflammation; hypertension

INTRODUCTION

High altitude (HA) is defined as a height between 2000 and 4000 m above sea level; very high altitude is between 4000 and 5500 m, and altitudes >5500 m are considered extremely high altitudes. The lower pressures noticed at high-altitudes lead to extreme conditions for humans to endure due to the lack of oxygen and low pressure of the atmosphere, which leads to hypobaric hypoxia (Zafren, 2013). This leads to a multitude of effects (mainly as a result of hypoxia) that have been confirmed to arise from different immunological and genetic changes which unconditioned travelers to high altitudes could experience (Kim et al. 2006; Witt et al. 2006)This has led to a new category of illnesses, known as "high-altitude illnesses" (HAS), which is then divided into "acute altitude illnesses" and "chronic altitude illnesses" depending on the length of a person's stay at high latitudes. HAS dramatically affects travelers and hikers, but the main prey of these illnesses is soldiers, which don't have the time to slowly adapt to the environment they've been deployed in (R. Chen et al. 2021; A. Jha et al. 2020; Kumar & Singh, 2018).

Acute altitude illness (AAS) is a blanket term that encompasses 3 diseases that are regularly encountered at high enough elevations: acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE) [11]. On the other hand, chronic mountain sickness is divided into 3 different parts, namely high-altitude polycythemia (HAPC), high-altitude heart disease (HAHD), and mixed chronic mountain sickness (MCMS), which includes both excessive polycythemia and pulmonary hypertension–related HAHD (Villafuerte et al. 2016). Variation in physiological responses to high altitudes has been noted in past studies, even when tested with the same variables in mind, which has created a new demand in high-altitude biology to understand the sources and reasons behind the variability in reactions (Pla et al. 2020 - Meehan et al. 1982) A recent potential source of such disparities is genetics, which has been greatly supported by the

apparent differences in susceptibility between populations, the notion that a history of altitude illness is indicative of subsequent risk, the heritability of hypoxia-related traits, and the association of specific genetic variants with susceptibility to altitude illness (MacInnis et al. 2016 - MacInnis et al. 2010) HAS could also be associated with immunological responses which will be discussed in this present review (Beall , 2016 - Khanna et al. 2017).

2. Acute Altitude Illnesses

Acute altitude illness is a term compromising of 3 ailments: Acute Mountain Sickness, High-altitude Cerebral Edema, and High-altitude Pulmonary Edema. All of them typically occur at altitudes starting at 2,500 meters and above (Carod-Artal , 2014). AMS is considered very common amongst unacclimatized travelers, whilst HACE and HAPE are much rarer (Imray et al. 2014; Luks et al. 2014). . It is also important to note that these illnesses widely vary according to environmental and genetic factors.

2.1. Acute Mountain Sickness (AMS)

AMS is a syndrome caused by the rapid ascension to altitudes typically above 2500 meters (Mirrakhimov et al. 2016; (Carod-Artal , 2014); (Imray et al. 2014); (Imray et al. 2010;], although the aforementioned variability may lead to earlier or later onsets depending on the individual's history, acclimation, and genes (Imray et al. 2010; Guobjartsson et al. 2019; Li et al. 2018). It's subjective because of its lack of pathognomic clinical signs, but is usually characterized by the presence of a headache (commonly known as high altitude headache (HAH)) alongside one or more of the following symptoms: loss of appetite, nausea, vomiting, fatigue, weakness, dizziness, light-headedness or sleep disturbance (Hackett and Roach , 2001; Villafuerte and Corante 2016; Pla et al. 2020; Guobjartsson et al. 2019; Li et al. 2018; Meehan and Zavala 1982; MacInnis and Koehle 2016; Villca et al. 2021; MacInnis et al. 2010; Beall 2014; Pham et al. 2021; Khanna et al. 2017; Carod-Artal 2014; Imray et al. 2010; Luks et al. 2019). Furthermore, assessing AMS had been an important goal for scientists aiming to study it, which has led to 2 widely-spread assessments: the Lake Louise Score (LLS) (Roach et al. 2018) and the much older AMS-C score of the Environmental Symptom Questionnaire (ESQ) (Sampson et al. 1983). The main difference between the 2 evaluations is that the LLS recognizes mild AMS at an earlier stage (mainly HAH), whilst AMS recognized by the ESQ is more advanced and immense. Prevention of AMS mainly comes in the form of acclimatization and slow-ascent, which can reportedly reduce its symptoms five-fold (Forster 1984; Robinson and King , 1971; Schneider et al. 2002; Bärtsch et al. 2004). A controversial topic that has been discussed in the context of AMS has been its correlation with old age. Although speculations in the past that had to do with the decrease in brain size in older individuals led to the hypothesis of a negative correlation between age and AMS, new studies have attested that age isn't associated with the development of acute mountain sickness (Roach et al. 1995; Small et al. 2022). Additionally, a recent review showed the correlation between AMS and HACE, syndromes that have been believed to lead to each other, and determined that there is no direct relationship between them (Turner et al. 2021; Zafren , 2014). This is consistent with the studies that have determined HACE to be caused by an increase in brain water (vasogenic edema), something that doesn't characterize AMS (Turner et al. 2021; Jha et al. 2019). AMS, however, can be considered important precursors to ionic and/or vasogenic edema, and consequently, HACE (Liang et al. 2007; Stokum et al. 2016). It has also been suggested that a neurooxidative basis for AMS is plausible because of the vulnerable cerebrovascular endothelium and underlying vasculature, which are easily susceptible to redox reactions that are amplified in high altitudes (Gaur et al. 2021; Larson et al. 1982).

2.2. High-altitude Cerebral Edema (HACE)

High-altitude cerebral edema is a rare, extreme syndrome that is mainly characterized by confusion, behavioral abnormalities, ataxia, altered consciousness, papilledema, brain edema, and brain ischemia (Hackett et al. 2001; Aksel et al. 2019). It is associated with extracellular edema inside the genu and splenium of the corpus callosum according to new neuroimaging studies (Hackett et al. 1998; Schommer et al. 2013). Microbleeds within white matter in the brain have also been identified through susceptibility-weighted neuroimaging (SWI) on HACE survivors; moreover, these microbleeds were only clear in individuals who had survived HACE with no prior exposure to AMS (Hackett et al. 2019). Moreover, as discussed before, it is important to note that although the pathophysiology of AMS and HACE intersect at many points, there has yet to be any direct correlation between them (Imray et al. 2010).

The glymphatic system is a network of perivascular tunnels that let through cortical interstitial solutes that are received from the brain via convective flow. This system can be affected by hydrostatic pressure (arterial and CSF pulsation), vasomotor contractions, adrenergic signaling, posture, and sleep [Iliff et al. 2013, Iliff et al. 2013, Lee et al. 2015, Fultz et al. 2019, Xie et al. 2013), all of which are factors that could affect HACE. For example, prolonged hypoxemia can cause cerebral vasodilation (Wilson et al. 2011, Arngrim et al. 2016, Willie et al. 2014, Imray et al. 2017), mild arterial hypertension (Imray et al. 2017, Rhodes et al. 2020, Wilson et al. 2011), and sympathetic hyperactivity (Imray et al. 2017, Rhodes et al. 2020). Another apparent cause for HACE according to magnetic resonance imaging screenings is reversible vasogenic and cytotoxic edema that progresses to microvascular disruption, which consequently turns into microbleeds that lead to HACE.

2.3. High-altitude Pulmonary Edema (HAPE)

High Altitude Pulmonary Edema (HAPE) is a fatal noncardiogenic pulmonary edema that occurs after extended exposure to hypoxia. Unlike AMS, it is clinically characterized by fatigue, dyspnea, and dry cough with exertion; however, it could progress to dyspnea at rest, rales, cyanosis, and a mortality rate of up to 50% (Nieto Estrada et al. 2017; Gonzalez Garay et al. 2018; Woods and Alcock 2021). It is additionally noted that HAPE usually happens in altitudes above 2,500 meters but can happen in altitudes as low as 2,000 meters due to factors such as low hypoxic ventilatory response (HVR), the altitude attained, a rapid rate of ascent, male sex, use of sleep medication, excessive salt ingestion, ambient cold temperature, heavy physical exertion, and preexisting conditions that leave their owners more susceptible to pulmonary edema (e.g. increased pulmonary blood flow and pulmonary hypertension) (Khodaee et al. 2016; Nieto Estrada et al. 2017; Woods and Alcock 2021). At altitude, the pulmonary vasculature, and the extent of the body, responds to hypoxia by hyperventilation, which is known as the hypoxic ventilator response (HVR).

3. Chronic Altitude Illnesses (CAI)

It is currently approximated that there are more than 140 million people worldwide who are currently at an altitude of over 2,500 meters. This leads them to chronic hypoxia, which is accompanied by various changes in the human body, with the most relevant changes occurring in the cardiopulmonary circuit, particularly in the right circuit. CAI is commonly divided into Chronic mountain sickness and High altitude pulmonary hypertension; however, it is important to note that since both of these diseases only affect some people living in high altitudes, genetic factors play an immense role in each of their pathogenesis processes (Mirrakhimov and Strohl , 2016).

3.1. Chronic Mountain Sickness (CMS)

Unlike AMS, CMS, also known as Monge's disease, is a clinical syndrome that occurs in long-time residents of high-altitude places above 2,500 meters. It is often characterized by excessive erythrocytosis/polycythemia (females Hb >= 19 g/dL; males Hb >= 21 g/dL), severe hypoxemia, and in some cases moderate or severe pulmonary hypertension (Taylor , 2011). Such clinical symptoms usually disappear after a gradual descent. It is often measured by the Qinghai Score (León-Velarde et al. 2005).

3.2. High Altitude Pulmonary Hypertension (HAPH)

In general, pulmonary hypertension (PH) is a blanket term used to describe a group of disorders characterized by a mean pulmonary arterial pressure ≥25 mm Hg on right heart catheterization. It's divided into 5 groups for classification: (1) pulmonary arterial hypertension, (2) PH owing to left heart disease, (3) PH owing to lung diseases and/or hypoxia, (4) Chronic Thromboembolic PH, (5) PH with unclear multifactorial mechanisms (Simonneau et al. 2009; Simonneau et al. 2018). HAPH is included in the 3rd classification group (Simonneau et al. 2009). It is caused by pulmonary vasoconstriction and the increase in pulmonary vascular resistance experienced in hypoxic environments (e.g. high altitudes), and such a physiological response is done by the body to improve blood flow, reduce perfusion of poorly ventilated lung areas, and leadsto vascular remodeling at the level of small pulmonary arteries and veins. Such arteries and veins are usually devoid of smooth muscle, but hypoxia has been shown to stimulate the proliferation of smooth muscle cells from the local myofibroblasts, and such changes remain even after returning to normoxia (Mirrakhimov and Strohl 2016; Oswald-Mammosser et al. 1995; Sobin et al. 1983). Vascular remodeling also decreases apoptosis of these smooth muscle cells and modulates the biochemical activity of pulmonary endothelium towards a direction concerned with the production of endothelin-1.

4. Genetic Effects

Genetic factors have been a major determinant of the intensity of different HAS (Simonson et al. 2010). In this review, we will be discussing the most well-documented genes that affect such ailments and their polymorphisms whilst enumerating each of their reported uses.

4.1. Hypoxia-Inducible Factor 1α (HIF-1α)

HIF-1α is a regulatory protein heterodimer that has developed a reputation as the maestro behind the transcriptional response to hypoxia, specifically to minimize hypoxic injury and restore adequate oxygenation. One of its main mechanisms, for example, is the creation and formation of erythropoietin (EPO), which elevates tissue O2 concentration to counteract the injury of hypoxia. Furthermore, although a few studies have shown that HIF-1α can be induced via the PI3-kinase/AKT/mTOR pathway (Lee et al. 2015; Marhold et al. 2015), the induction mechanisms have yet to be fully understood. Studies have also shown strong HIF-1α expressions in the epithelial cells and vascular endothelial cells of intestinal tissues in high-altitude rats due to the low oxygen environment — something that was completely absent in rats living in low-latitudes (Zhang et al. 2015). Additionally, it is worth noting that the α subunits of HIF-1α are what make it O2 sensitive.

Additionally, HIF-1α may have pathogenic roles in pulmonary hypertension due to its ability to regulate distinct cellular processes in pulmonary artery endothelial cells [84–87]. Damage to such cells can then lead to susceptibility to HAPE. Additionally, HIF-1α may have pathogenic roles in pulmonary hypertension due to its ability to regulate distinct cellular processes in pulmonary artery endothelial cells (Pullamsetti et al. 2020; Tan et al. 2013; Gale et al. 2008; Shimoda and Laurie 2014). Damage to such cells can then lead to susceptibility to

HAPE. In general, HIF activity is controlled by the environment's oxygen concertation via site-specific prolyl hydroxylation of the α subunit, making hydroxylation the key post-translational modification regulating HIF activity. In HIF-1α, the primary site of hydroxylation is on Pro564, and that leaves a platform for Von-Hippel-Lindau (VHL)-Ubiquitin Ligase to degrade the hydroxylated HIF-1α using the ubiquitin-proteasome pathway. It is also important to note that HIF-2α and HIF-1α often act in the same direction; for example, both of them have equal capacity to activate the VEGFA gene, which encodes for a key angiogenesis protein (Keith et al. 2011). HIF-1α polymorphisms have been extensively studied in the past, and so far, we have many polymorphisms to analyze and associate with diseases. For example, HIF-1α C1772T and G1790A have been recently confirmed to be polymorphisms associated with head and neck cancer (Wu et al. 2021; Konac et al. 2007). HIF-1A Pro582Ser is strongly correlated to resistance against the development of diabetic nephropathy and proved to reduce the risk of diabetes in the Japanese population, whilst HIF1A Ala588Thr showed little to no effect (Ren et al. 2020; Gu et al. 2013; Catrina and Zheng 2021).

4.2. EPAS1 (Hypoxia-Inducible Factor 2α (HIF-2α)

HIF-2α presents 48% amino acid sequence homology with HIF-1α with a similar domain arrangement, and although they both share similar characteristics (e.g. domain structure, heterodimerize with HIF-1β, and bind to the same DNA sequence called hypoxia-responsive element (HRE)), HIF-2α is involved in the regulation of genes important for tumor growth, HAPH progression, cell cycle progression and maintaining stem cell pluripotency, like the protooncogene MYC (which it co-operates with), whilst HIF-1α is concerned with regulating and inducing glycolytic responses and antagonizing the MYC protooncogene. (Keith et al. 2011; Wu et al. 2021; Konac et al. 2007; Ren et al. 2020; Gu et al. 2013; Catrina and Zheng 2021). Another difference between HIF-1α and HIF-2α is their functions; HIF-1α promotes cell cycle arrest/halt, whilst HIF-2α promotes progression through the cell cycle, leading to the belief that HIF-2α is more directly associated with tumor progression than HIF-1α. (Loboda et al. 2012; Wang et al. 2005; Hu et al. 2007; Gordan et al. 2007; Barontini and Dahia 2014). Another gene that HIF-2α regulates is EPO in interstitial cells in the adult kidney, which produces EPO, a red blood cell regulator. This is consistent with other studies that have proposed that a lack of HIF-2α is accompanied by anemia, whilst an excess of it is accompanied by erythrocytosis (Scortegagna et al. 2005, Tan et al. 2013, Gruber et al. 2007). There is a lot of evidence of its presence in high-altitude individuals and rats, leading scientists to hypothesize its involvement in counteracting the hypoxia presented in high altitudes by overexpressing HIF-2α, consequently leading to a greater RBC count and stabilizing hypoxia. (Simonson et al. 2010, Xu et al. 2011, Bigham et al. 2010, Beall et al. 2010, Bigham and Lee 2014).

Recent studies have also shown that the SNPs EPAS1_rs4953354 and EPAS1_rs6756667 strongly correlate to decreased risk of HAH; additionally, it has been speculated that these genes may be able to alter transcription factors' binding receptors and be in linkage disequilibrium with other true functional SNPs, which would consequently regulate HIF regulation and EPAS1 expression. Such polymorphisms were strongly present in Tibetan populations probably due to natural selection (Simonson et al. 2010, Bigham et al. 2011).

4.3. Vascular Endothelial Growth Factor (VEGF)

VEGF is an endothelial cell-specific mitogen and angiogenic permeability factor and is mainly modulated by HIF-1. It works by binding itself to a receptor in the cell and increasing its permeability and changing the cell's structure, consequently leading to edema and AMS if overexpressed in the lungs (Fan et al. 2020; Liang et al. 2014; Hanaoka et al. 2003). Such an overexpression can be achieved through hypoxia, and maybe a pathophysiological part in the development of HAPE (Hanaoka et al. 2003; Christou et al. 1998; Liu et al. 1995; Tuder et al. 1995). It has also been hypothesized that VEGF expression could be a cause for HACE because it tended to increase extracerebral capillary permeability, leading to edema (Xu and Severinghaus 1998). Recent studies have shown that polymorphisms in the genes of VEGF, particularly VEGF-2578C/A rs699947, are considered a risk factor for diabetic retinopathy, bladder cancer, and renal cell carcinoma, whilst not affect prostate cancer (Song et al. 2018 - Wijaya et al. 2021). Three particular alleles were found to play a role in this polymorphism, mainly A, C, and T. The C allele was observed to be a factor in developing diabetic retinopathy, whilst T and A were protective factors of the disease.

4.4. Tumor Suppressor P53

P53 is a tumor suppressor protein that inhibits the transformation and mutation of cells by viral and/or cellular oncogenes. It is transcript through the gene TP53 and is activated in response to stress, and more importantly, hypoxia (Royds et al. 1998; Zhao et al. 2013; Humpton and Vousden , 2016; Amelio and Melino , 2015; Blagih et al. 2020). It induces various forms of cell death or senescence, which lead to its ability to suppress tumors effectively (Vogelstein et al. 2000; Kastenhuber and Lowe , 2017; Vousden and Prives , 2009).

The effects of hypoxia and high-altitude environments on P53 regulation and expression have been extensively studied in the past. For example, Serine-15 (Ser-15) is the primary target of p53's DNA damage response and is usually phosphorylated by both the ATM and ATR protein kinases (Loughery et al. 2014), and studies have shown that severe hypoxia does lead to phosphorylation of Ser-15 and others have shown a sharp increase in p53

presence at both the microRNA and protein levels in hepatocytes (Jacovas et al. 2018; Koumenis et al. 2001; Zhao et al. 2013). This is consistent with the common risks associated with high altitude travel in chronic liver disease patients which can lead to fibrosis, a phenomenon that has been linked with an increase in p53 in mice liver (Luks and Swenson 2015; Kodama et al. 2011; Ramsoe et al. 1970).

These results in p53 increases due to hypoxia, however, were only present in extreme altitudes (7,000+ meters) when tested for 8 hours. Additionally, it has also been noted that the type-1 corticotrophin-releasing hormone (CRHR1) mediates p53 expression and transcription, as it has been determined that the CRHR1 antagonist CP-154,526 was one of the key reasons p53 didn't notice a steady increase at altitudes below 7,000 meters (Zhao et al. 2013).

A study also argued that the suppression of certain apoptotic genes would lead to a higher risk of developing malignant tumors (Voskarides , 2018). This suppression is most evident in both high-altitude and cold areas and is apparent in the Inuit, who have the highest incidence of colorectal cancer in the world (Young et al. 2016). Additionally, the blind mole rat, Spalax Ehrenberg, has an overexpression of p53 molecules, which proposes it as a potential mechanism to counteract the hypoxia it experiences and the tumors that may come with it (Voskarides , 2018).

Germline mutations in TP53 could increase the risk of certain types of cancers, such as breast cancer, leukemia, soft tissue sarcomas, CNS tumors, and adrenocortical cancer (Li and Fraumeni 1969). Certain studies have, however, shown that patients with breast cancer had a high frequency of somatic TP53 mutations (Langerød et al. 2007; Daly et al. 2021). These mutations can also be caused by SNPs, and the most frequently reported SNP in TP53 is TP53_ rs1042522. It has two main variants: Arg72 or Pro72, and it's located at the second position of codon 72 in exon 4. Both of these variants serve roles in various types of cancer, but it has been reported that the Arg72 variant is more efficient at inducing apoptosis because of its greater ability to interact with MDM2 (Dumont et al. 2003; Dahabreh et al. 2013).

4.5. Von-Hippel-Lindau (VHL)-Ubiquitin Ligase

VHL disease is a syndrome characterized by increased vulnerability and susceptibility to several malignancies, including renal cell carcinoma, hemangioblastomas of the central nervous system or retina, and phaeochromocytomas. It is encoded by the VHL tumor gene, which is an E3 ubiquitin ligase that maps to chromosome 3p25 (Latif et al. 1993). It targets proteasome degradation and has two subdomains: the alpha domain, which works to degrade proteosomes, and the beta domain, which works as a substrate-docking site. Hydroxylated alpha subunits in HIF are known to be one of the most well-known substrates for the beta domain of VHL and usually degrade once they react with VHL.

VHL disease is a syndrome characterized by increased vulnerability and susceptibility to several malignancies, including renal cell carcinoma, hemangioblastomas of the central nervous system or retina, and phaeochromocytomas. It is encoded by the VHL tumor gene, which is an E3 ubiquitin ligase that maps to chromosome 3p25 (Latif et al. 1993). It targets proteasome degradation and has two subdomains: the alpha domain, which works to degrade proteosomes, and the beta domain, which works as a substrate-docking site. Hydroxylated alpha subunits in HIF are known to be one of the most well-known substrates for the beta domain of VHL and usually degrade once they react with VHL.

In mutant VHL target tissues, however, HIF activity sharply increases because of the lack of modulation by VHL, leading to multiple transcriptional activations of HIF target genes (e.g. angiogenic factors such as VEGF and enzymes concerned with glucose metabolism) (Zhang & Zhang 2018). As discussed before, HIF-2α has been proven to be more influential in tumor progression when compared to HIF-1α. This has led scientists to propose that the overexpression in HIF-2α when a mutant VHL target tissue is present is what causes the susceptibility observed in the VHL disease. This relationship between VHL and HIF gene expressions has created two separate categories of VHL effects: HIF-dependent effects of VHL and HIF-independent VHL functions.

HIF-dependent effects of VHL include Epithelial-mesenchymal transition (EMT) and Reactive oxygen species (ROS). EMT contributes to renal development, fibrosis, and cancer. VHL malfunction can lead to disruptions in various EMT processes which are believed to contribute to the tumorigenic process (Gläsker et al. 2020; Hapke & Haake 2020). On the other hand, ROS regulates hypoxia-dependent and hypoxia-independent activation of HIF-1α (Guzy et al. 2005; Kaelin 2005; Brunelle et al. 2005).

HIF-independent effects of VHL include primary cilium integrity (associated with cyst development), extracellular matrix function (causes increased tumor angiogenesis), apoptosis, and senescence (Barontini & Dahia 2010; Stickle et al. 2005). VHL's canonical E3 ligase function lets it control many substrates including NDRG3, G9a, and EpoR that let it have this wide range of pathophysiological phenomena.

Furthermore, germline polymorphism assessments have shown that people carrying at least one variant allele for the VHL_rs779805 SNP have been proven to have significantly more risk for renal cell carcinoma (RCC) and clear-cell renal cell carcinoma (ccRCC). Other SNPs that have been studied showed little to no correlation, and those included VHL_rs164239, VHL_rs265318, and HIF1A_rs2301111 (van de Pol et al. 2020). Another study proposed the VHL_rs1642742 CC genotype and the VHL_rs1642743 GG genotype as potential biomarkers to determine a person's vulnerability to metastatic ccRCC

after being treated with first-line vascular endothelial growth factor receptor (VEGFR), but confirmation would need further research (Verbiest et al. 2018).

5. Immunological Effects

Most of the immunological effects noticed at high altitudes are due to hypoxia and are usually caused and counteracted by gene mutations and natural selection.

5.1. Immune-Mediated Inflammatory Diseases (IMIDs*)*

When the body is attacked by pathogens via infection from a wound, it attacks said pathogens with secreted proinflammatory cytokines and cytotoxic molecules and/or by direct cell-mediated cytotoxicity (Hawiger et al. 2001; Robertson , 2007). This attack may also result in undesirable outcomes, such as collateral tissue damage (inflammation) (Sitkovsky et al. 2004). Such uncontrolled inflammation could lead to the pathogenesis of major diseases including cancer, heart disease, atherosclerosis, and sepsis (Gao and Hong , 2008; Erjefält , 2019; Lin et al. 2018); however, the body has come up with a way to counteract this with “nonimmune” molecules that inhibited immune cells to prevent such collateral damage (Fanelli et al. 2018; Leigh et al. 2020).

Many studies have shown that hypoxia and the HIF response influence the initiation of autoimmune responses and contribute to the development of dysfunctions in autoimmunity and cancer. Thus, pharmaceutical companies have been targeting specific HIF proteins (e.g. HIF-1α and HIF-2α) because of their significance in mediating and controlling inflammations and IMIDs (Chen et al. 2021).

Furthermore, HIF-1α’s involvement in the immune system continues to extend as it has been proven to be influential in regulating development, survival, proliferation, and differentiation in not only human T and B cells, but also virtually all innate and adaptive immune cell populations (Chen et al. 2021; Biju et al. 2004; Shi et al. 2011; Dang et al. 2011; Makino et al. 2003; Cramer et al. 2003; Walmsley et al. 2005). HIF-2α, on the other hand, was shown to be active in certain immune cells such as in tumor-associated macrophages, in vitro expanded CD8+ T cells, and in response to cytokines and hypoxia (Zinkernagel et al. 2007; Palazon et al. 2014). Do note, however, that HIF-α in general can be induced by a variety of inflammatory stimuli such as bacterial products, leading to the proposal that HIFs and hypoxia are considered one of our body’s immediate responses to inflammation to prevent collateral damage that could lead up to pathogenesis of fatal illnesses (Chen et al. 2021). High altitude effects on IMIDs explain the countless case studies on high altitude correlations with cancer, asthma, and edema (Eichner et al. 2018; Moore et al. 2019; Sallusto et al. 2019; Zhang et al. 2019; Singh et al. 2020).

5.2. Gastrointestinal Tract

Different studies on humans and animals have determined that geographical altitude does have a pronounced effect on fecal microbiota, although some argue that human results may be subject to limitations as fecal microbiota could also be influenced by diet and genetic background (Power et al. 2014; Li and Zhao , 2015). Studies on rats have shown a correlation between high-altitude hypoxia environmental and an increase in the relative abundance of genera Alistipes, which is associated with gut inflammation, chronic fatigue syndrome, and more recently, e-hypoxia-induced intestinal disorders (Zhang et al. 2018; Frémont et al. 2013; Naseribafrouei et al. 2014). Additionally, the genera Heliobacter, the majority species of which are suspected to be gastrointestinal pathogens, was found to be reduced in terms of abundance (Fox , 1997). Other microbiotas that were found to decrease in abundance as hypoxia levels increased are Epsilonproteobacteria, phylum Actinobacteria, and class Erysipelotrichia (Liu et al. 2014; den Hengst and Buttner , 2008).

One of the most vulnerable yet fundamental immune response systems is the mucosal immune system, formally known as MALT (Mucosa Associated Lymphoid Tissue). MALT is usually located in organ linings and contains lymphoid cells that can protect the body from harmful pathogens (Ak et al. 2021; Xie et al. 2019; Kiesewetter and Raderer, 2020; Khanna et al. 2018). A study on humans has shown, however, that Secretory immunoglobulin A (sIgA), a major immunoglobulin of the mucosal immune system, levels decrease as hypoxia and overall physical exercise increase (Tiollier et al. 2005).

Other effects of high altitude on the GI tract include an increased risk of upper GI tract bleeding when exposed to 5,000 meters and non-functioning mucosal barriers (Bletz et al. 2013; Ak et al. 2021; Khanna et al. 2018).

5.3. Sleep Disturbances

High altitudes are characterized by hypoxia and low concentrations of oxygen sustained exposure of which could lead to effects on body weight, muscle structure, exercise capacity, mental functioning, and sleep quality (San et al. 2013). It induces high-altitude periodic breathing (PB), which is a breathing pattern distinguished by breathing instability, with periods of deep and rapid breathing alternating with central apnea. Surprisingly, such a pattern is noticeable in perfectly healthy individuals at altitudes above 6,000 ft. and may lead to difficulties in sleeping (e.g. frequent arousals and daytime somnolence). Furthermore, it leads to depressive moods, anger, and fatigue alongside a decrease in vigor, attention, memory, concentration, executive functions, and speed of mental processing (San et al. 2013; Kabel et al. 2018; Weil , 2004). These alternating periods of deep breathing and shallow breathing caused by PB can cause instability in blood oxygen levels, which leads scientists to hypothesize that high-altitude sleep disturbances are associated with hypoxemia and PB (Taylor 2011; Nussbaumer-Ochsner et al. 2012; San et al. 2013).

CONCLUSION

In conclusion, HAS are ailments that are greatly affected by genetic and environmental factors and are categorized into acute and chronic altitude illnesses. The former is further categorized into AMS, HAPE, and HACE, whilst the latter is divided into CMS and HAPH. They're all mainly caused by physiological responses of our body to the low oxygen concentration present in high altitudes and are expressed and amplified by different genes. Prevention and treatment of such illnesses would be to simply ascend with caution or descend until symptoms are alleviated. However, failure to treat mildAMS could escalate to fatal cases of HAPE or HACE when left untreated. Genetic factors, in particular, are what enabled Tibetan and Inuit populations to adapt to their harsh, high environments that caused them many illnesses. We discussed the functions and associations of different genes, namely VHL, P53, VEGF, HIF-1α, and HIF-2α.

It was also noted how different immunological effects induced by different genes, mainly hypoxia and HIF-responses' induction of autoimmune diseases, hypoxia's direct correlation with different intestinal disorders, and hypoxia's association with periodic breathing, which consequently causes sleep disturbances.

CONFLICT OF INTEREST.

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors contributed equally and have been involved in the writing of the manuscript at draft, any revision stages, and have read and approved the final version.

REFERENCES

Ak, T.P. Bronchus-Associated Lymphoid Tissue (BALT) Histology and Its Role in Various Pathologies. 2021, doi:10.5772/INTECHOPEN.99366.

Aksel, G.; Çorbacıoğlu, Ş.K.; Özen, C. High-Altitude Illness: Management Approach. *Turk J Emerg Med*2019, *19*, 121–126, doi:10.1016/J.TJEM.2019.09.002.

Amelio, I.; Melino, G. The P53 Family and the Hypoxia-Inducible Factors (HIFs): Determinants of Cancer Progression. *Trends Biochem Sci*2015, *40*, 425–434, doi:10.1016/J.TIBS.2015.04.007.

Arngrim, N.; Schytz, H.W.; Britze, J.; Amin, F.M.; Vestergaard, M.B.; Hougaard, A.; Wolfram, F.; de Koning, P.J.H.; Olsen, K.S.; Secher, N.H.; et al. Migraine Induced by Hypoxia: An MRI Spectroscopy and Angiography Study. *Brain*2016, *139*, 723–737, doi:10.1093/BRAIN/AWV359.

Avancini, A.; Belluomini, L.; Tregnago, D.; Trestini, I.; Milella, M.; Lanza, M.; Pilotto, S. Exercise and Anemia in Cancer Patients: Could It Make the Difference? *https://doi.org/10.1080/17474086.2021.20077642*2021, *14*, 979–985, doi:10.1080/17474086.2021.2007764.

Barontini, M.; Dahia, P.L.M. VHL Disease. *Best Pract Res Clin Endocrinol Metab*2010, *24*, 401–413, doi:10.1016/J.BEEM.2010.01.002.

Barontini, M.; Dahia, P.L.M. VHL Disease. *Best Pract Res Clin Endocrinol Metab*2010, *24*, 401–413, doi:10.1016/J.BEEM.2010.01.002.

Bärtsch, P.; Bailey, D.M.; Berger, M.M.; Knauth, M.; Baumgartner, R.W. Acute Mountain Sickness: Controversies and Advances. *High Alt Med Biol*2004, *5*, 110–124, doi:10.1089/1527029041352108.

Basnyat, B.; Murdoch, D.R. High-Altitude Illness. *Lancet*2003, *361*, 1967–1974, doi:10.1016/S0140-6736(03)13591-X.

Beall, C.M. Adaptation to High Altitude: Phenotypes and Genotypes. *http://dx.doi.org/10.1146/annurev-anthro-102313-0300002*014, *43*, 251–272, doi:10.1146/ANNUREV-ANTHRO-102313-030000.

Beall, C.M.; Cavalleri, G.L.; Deng, L.; Elston, R.C.; Gao, Y.; Knight, J.; Li, C.; Li, J.C.; Liang, Y.; McCormack, M.; et al. Natural Selection on EPAS1 (HIF2alpha) Associated with Low Hemoglobin Concentration in Tibetan Highlanders. *Proc Natl Acad Sci U S A*2010, *107*, 11459–11464, doi:10.1073/PNAS.1002443107.

Bigham, A.; Bauchet, M.; Pinto, D.; Mao, X.; Akey, J.M.; Mei, R.; Scherer, S.W.; Julian, C.G.; Wilson, M.J.; Herráez, D.L.; et al. Identifying Signatures of Natural Selection in Tibetan and Andean Populations Using Dense Genome Scan Data. *PLoS Genet*2010, *6*, doi:10.1371/JOURNAL.PGEN.1001116.

Bigham, A.W.; Lee, F.S. Human High-Altitude Adaptation: Forward Genetics Meets the HIF Pathway. *Genes Dev*2014, *28*, 2189, doi:10.1101/GAD.250167.114.

Biju, M.P.; Neumann, A.K.; Bensinger, S.J.; Johnson, R.S.; Turka, L.A.; Haase, V.H. Vhlh Gene Deletion Induces Hif-1-Mediated Cell Death in Thymocytes . *Mol Cell Biol*2004, *24*, 9038–9047, doi:10.1128/MCB.24.20.9038-9047.2004/SUPPL_FILE/SUPPLEMENTAL_DATA.PDF.

Bilo, G.; Caldara, G.; Styczkiewicz, K.; Revera, M.;

Lombardi, C.; Giglio, A.; Zambon, A.; Corrao, G.; Faini, A.; Valentini, M.; et al. Effects of Selective and Nonselective Beta-Blockade on 24-h Ambulatory Blood Pressure under Hypobaric Hypoxia at Altitude. *J Hypertens*2011, *29*, 380–387, doi:10.1097/HJH.0B013E3283409014.

Blagih, J.; Buck, M.D.; Vousden, K.H. REVIEW SPECIAL ISSUE: CELL BIOLOGY OF THE IMMUNE SYSTEM P53, Cancer and the Immune Response. 2020, doi:10.1242/jcs.237453.

Bletz, M.C.; Loudon, A.H.; Becker, M.H.; Bell, S.C.; Woodhams, D.C.; Minbiole, K.P.C.; Harris, R.N. Mitigating Amphibian Chytridiomycosis with Bioaugmentation: Characteristics of Effective Probiotics and Strategies for Their Selection and Use. *Ecol Lett*2013, *16*, 807–820, doi:10.1111/ELE.12099.

Boonpiyathad, T.; Capova, G.; Duchna, H.W.; Croxford, A.L.; Farine, H.; Dreher, A.; Clozel, M.; Schreiber, J.; Kubena, P.; Lunjani, N.; et al. Impact of High-Altitude Therapy on Type-2 Immune Responses in Asthma Patients. *Allergy*2020, *75*, 84–94, doi:10.1111/ALL.13967.

Brunelle, J.K.; Bell, E.L.; Quesada, N.M.; Vercauteren, K.; Tiranti, V.; Zeviani, M.; Scarpulla, R.C.; Chandel, N.S. Oxygen Sensing Requires Mitochondrial ROS but Not Oxidative Phosphorylation. *Cell Metab*2005, *1*, 409–414, doi:10.1016/J.CMET.2005.05.002.

Calderón - Gerstein, W.S.; Torres - Samaniego, G. High Altitude and Cancer: An Old Controversy. *Respir Physiol Neurobiol*2021, *289*, 103655, doi:10.1016/J.RESP.2021.103655.

Carod-Artal, F.J. High-Altitude Headache and Acute Mountain Sickness. *Neurología (English Edition)*2014, *29*, 533–540, doi:10.1016/J.NRLENG.2012.04.021.

Catrina, S.B.; Zheng, X. Hypoxia and Hypoxia-Inducible Factors in Diabetes and Its Complications. *Diabetologia*2021, *64*, 709–716, doi:10.1007/S00125-021-05380-Z/FIGURES/2.

Chen, R.; Wang, Y.; Zhang, C.; Luo, X.; Yang, J.; Liu, C.; Huang, L. Assessment of Acute Mountain Sickness Using 1993 and 2018 Versions of the Lake Louise Score in a Large Chinese Cohort. *https://home.liebertpub.com/ham*2021, *22*, 362–368, doi:10.1089/HAM.2021.0031.

Chen, Y.; Gaber, T. Hypoxia/HIF Modulates Immune Responses. *Biomedicines*2021, *9*, doi:10.3390/BIOMEDICINES9030260.

Christou, H.; Yoshida, A.; Arthur, V.; Morita, T.; Kourembanas, S. Increased Vascular Endothelial Growth Factor Production in the Lungs of Rats with Hypoxia-Induced Pulmonary Hypertension. *Am J Respir Cell Mol Biol*1998, *18*, 768–776, doi:10.1165/AJRCMB.18.6.2980.

Cramer, T.; Yamanishi, Y.; Clausen, B.E.; Förster, I.; Pawlinski, R.; Mackman, N.; Haase, V.H.; Jaenisch, R.; Corr, M.; Nizet, V.; et al. HIF-1α Is Essential for Myeloid Cell-Mediated Inflammation. *Cell*2003, *112*, 645–657, doi:10.1016/S0092-8674(03)00154-5.

Dahabreh, I.J.; Schmid, C.H.; Lau, J.; Varvarigou, V.; Murray, S.; Trikalinos, T.A. Genotype Misclassification in Genetic Association Studies of the Rs1042522 TP53 (Arg72Pro) Polymorphism: A Systematic Review of Studies of Breast, Lung, Colorectal, Ovarian, and Endometrial Cancer. *Am J Epidemiol*2013, *177*, 1317–1325, doi:10.1093/AJE/KWS394.

Daly, M.B.; Pal, T.; Berry, M.P.; Buys, S.S.; Dickson, P.; Domchek, S.M.; Elkhanany, A.; Friedman, S.; Goggins, M.; Hutton, M.L.; et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*2021, *19*, 77–102, doi:10.6004/JNCCN.2021.0001.

Dang, E. v.; Barbi, J.; Yang, H.Y.; Jinasena, D.; Yu, H.; Zheng, Y.; Bordman, Z.; Fu, J.; Kim, Y.; Yen, H.R.; et al. Control of TH17/Treg Balance by Hypoxia-Inducible Factor 1. *Cell*2011, *146*, 772–784, doi:10.1016/J.CELL.2011.07.033/ATTACHMENT/BA9D04A0-0200-4B7B-A90F-C593F27168CB/MMC1.XLS.

den Hengst, C.D.; Buttner, M.J. Redox Control in Actinobacteria. *Biochimica et Biophysica Acta (BBA) - General Subjects*2008, *1780*, 1201–1216, doi:10.1016/J.BBAGEN.2008.01.008.

Duke, C.B.; Sallade, T.D.; Starling, J.; Pant, S.; Sheets, A.; McElwee, M.K.; Young, D.S.; Taylor, R.A.; Keyes, L.E. Hypertension and Acute Mountain Sickness in Himalayan Trekkers in Nepal: An Observational Cohort Study. *Wilderness Environ Med*2020, *31*, 157, doi:10.1016/J.WEM.2020.01.004.

Dumont, P.; Leu, J.I.J.; della Pietra, A.C.; George, D.L.; Murphy, M. The Codon 72 Polymorphic Variants of P53 Have Markedly Different Apoptotic Potential. *Nat Genet*2003, *33*, 357–365, doi:10.1038/NG1093.

Duplain, H.; Vollenweider, L.; Delabays, A.; Nicod, P.; Bärtsch, P.; Scherrer, U. Augmented Sympathetic Activation During Short-Term Hypoxia and High-Altitude Exposure in Subjects Susceptible to High-Altitude Pulmonary Edema. *Circulation*1999, *99*, 1713–1718, doi:10.1161/01.CIR.99.13.1713.

Erjefält, J.S. Unravelling the Complexity of Tissue Inflammation in Uncontrolled and Severe Asthma. *Curr Opin Pulm Med*2019, *25*, 79–86, doi:10.1097/MCP.0000000000000536.

Fan, N.; Liu, C.; Ren, M. Effect of Different High Altitudes on Vascular Endothelial Function in Healthy People. *Medicine*2020, *99*, e19292, doi:10.1097/MD.0000000000019292.

Fanelli, C.; Noreddin, A.; Nunes, A. Inflammation in Nonimmune-Mediated Chronic Kidney Disease. *Chronic Kidney Disease - from Pathophysiology to*

*Clinical Improvements*2018, doi:10.5772/INTECHOPEN.70611.

Fengping, X.U.; Severinghaus, J.W. Rat Brain VEGF Expression in Alveolar Hypoxia: Possible Role in High-Altitude Cerebral Edema. *J Appl Physiol (1985)*1998, *85*, 53–57, doi:10.1152/JAPPL.1998.85.1.53.

Forster, P. Reproducibility of Individual Response to Exposure to High Altitude. *Br Med J (Clin Res Ed)*1984, *289*, 1269–1269, doi:10.1136/BMJ.289.6454.1269.

Fox, J.G. The Expanding Genus of Helicobacter: Pathogenic and Zoonotic Potential. *Semin Gastrointest Dis*1997, *8*, 124–141.

Frémont, M.; Coomans, D.; Massart, S.; de Meirleir, K. High-Throughput 16S RRNA Gene Sequencing Reveals Alterations of Intestinal Microbiota in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients. *Anaerobe*2013, *22*, 50–56, doi:10.1016/J.ANAEROBE.2013.06.002.

Fultz, N.E.; Bonmassar, G.; Setsompop, K.; Stickgold, R.A.; Rosen, B.R.; Polimeni, J.R.; Lewis, L.D. Coupled Electrophysiological, Hemodynamic, and Cerebrospinal Fluid Oscillations in Human Sleep. *Science (1979)*2019, *366*, 628–631, doi:10.1126/SCIENCE.AAX5440/SUPPL_FILE/AAX5440_FULTZ_SM.PDF.

Gale, D.P.; Harten, S.K.; Reid, C.D.L.; Tuddenham, E.G.D.; Maxwell, P.H. Autosomal Dominant Erythrocytosis and Pulmonary Arterial Hypertension Associated with an Activating HIF2 Alpha Mutation. *Blood*2008, *112*, 919–921, doi:10.1182/BLOOD-2008-04-153718.

Gallagher, S.A.; Hackett, P.H. High-Altitude Illness. *Emerg Med Clin North Am*2004, *22*, 329–355, doi:10.1016/J.EMC.2004.02.001.

Gao, H.M.; Hong, J.S. Why Neurodegenerative Diseases Are Progressive: Uncontrolled Inflammation Drives Disease Progression. *Trends Immunol*2008, *29*, 357–365, doi:10.1016/J.IT.2008.05.002.

Gaur, P.; Prasad, S.; Kumar, B.; Sharma, S.K.; Vats, P. High-Altitude Hypoxia Induced Reactive Oxygen Species Generation, Signaling, and Mitigation Approaches. *Int J Biometeorol*2021, *65*, 601–615, doi:10.1007/S00484-020-02037-1/FIGURES/3.

Gläsker, S.; Vergauwen, E.; Koch, C.A.; Kutikov, A.; Vortmeyer, A.O. Von Hippel-Lindau Disease: Current Challenges and Future Prospects. *Onco Targets Ther*2020, *13*, 5669, doi:10.2147/OTT.S190753.

Gonzalez Garay, A.G.G.; Molano Franco, D.; Nieto Estrada, V.H.; Martí-Carvajal, A.J.; Arevalo-Rodriguez, I. Interventions for Preventing High Altitude Illness: Part 2. Less Commonly-Used Drugs. *Cochrane Database Syst Rev*2018, *3*, doi:10.1002/14651858.CD012983.

Gordan, J.D.; Bertout, J.A.; Hu, C.J.; Diehl, J.A.; Simon, M.C. HIF-2alpha Promotes Hypoxic Cell Proliferation by Enhancing c-Myc Transcriptional Activity. *Cancer Cell*2007, *11*, 335–347, doi:10.1016/J.CCR.2007.02.006.

Gruber, M.; Hu, C.J.; Johnson, R.S.; Brown, E.J.; Keith, B.; Simon, M.C. Acute Postnatal Ablation of Hif-2alpha Results in Anemia. *Proc Natl Acad Sci U S A*2007, *104*, 2301–2306, doi:10.1073/PNAS.0608382104.

Gu, H.F.; Zheng, X.; Seman, N.A.; Gu, T.; Botusan, I.R.; Sunkari, V.G.; Lokman, E.F.; Brismar, K.; Catrina, S.B. Impact of the Hypoxia-Inducible Factor-1 α (HIF1A) Pro582Ser Polymorphism on Diabetes Nephropathy. *Diabetes Care*2013, *36*, 415–421, doi:10.2337/DC12-1125.

Guan, J.; Long, K.; Ma, J.; Zhang, J.; He, D.; Jin, L.; Tang, Q.; Jiang, A.; Wang, X.; Hu, Y.; et al. Comparative Analysis of the MicroRNA Transcriptome between Yak and Cattle Provides Insight into High-Altitude Adaptation. *PeerJ*2017, *2017*, e3959, doi:10.7717/PEERJ.3959/SUPP-10.

Guobjartsson, T.; Sigurosson, E.; Gottfreosson, M.; Björnsson, Ó.M.; Guomundsson, G. [High Altitude Illness and Related Diseases - a Review]. *Laeknabladid*2019, *105*, 499–507, doi:10.17992/LBL.2019.11.257.

Guzy, R.D.; Hoyos, B.; Robin, E.; Chen, H.; Liu, L.; Mansfield, K.D.; Simon, M.C.; Hammerling, U.; Schumacker, P.T. Mitochondrial Complex III Is Required for Hypoxia-Induced ROS Production and Cellular Oxygen Sensing. *Cell Metab*2005, *1*, 401–408, doi:10.1016/J.CMET.2005.05.001.

Hackett, P.H.; Roach, R.C. High-Altitude Illness. *http://dx.doi.org/10.1056/NEJM200107123450206*2009, *345*, 107–114, doi:10.1056/NEJM200107123450206.

Hackett, P.H.; Roach, R.C. High-Altitude Illness. *N Engl J Med*2001, *345*, 107–114, doi:10.1056/NEJM200107123450206.

Hackett, P.H.; Yarnell, P.R.; Hill, R.; Reynard, K.; Heit, J.; McCormick, J. High-Altitude Cerebral Edema Evaluated With Magnetic Resonance Imaging: Clinical Correlation and Pathophysiology. *JAMA*1998, *280*, 1920–1925, doi:10.1001/JAMA.280.22.1920.

Hackett, P.H.; Yarnell, P.R.; Weiland, D.A.; Reynard, K.B. Acute and Evolving MRI of High-Altitude Cerebral Edema: Microbleeds, Edema, and Pathophysiology. *American Journal of Neuroradiology*2019, *40*, 464–469, doi:10.3174/AJNR.A5897.

Hakim, T.S.; Michel, R.P.; Minami, H.; Chang, H.K. Site of Pulmonary Hypoxic Vasoconstriction Studied with Arterial and Venous Occlusion. *J Appl Physiol Respir Environ Exerc Physiol*1983, *54*, 1298–1302, doi:10.1152/JAPPL.1983.54.5.1298.

Hanaoka, M.; Droma, Y.; Naramoto, A.; Honda, T.; Kobayashi, T.; Kubo, K. Vascular Endothelial Growth Factor in Patients with High-Altitude Pulmonary

Edema. *J Appl Physiol (1985)*2003, *94*, 1836–1840, doi:10.1152/JAPPLPHYSIOL.00575.2002.

Hansen, J.; Sander, M. Sympathetic Neural Overactivity in Healthy Humans after Prolonged Exposure to Hypobaric Hypoxia. *J Physiol*2003, *546*, 921–929, doi:10.1113/JPHYSIOL.2002.031765.

Hapke, R.Y.; Haake, S.M. Hypoxia-Induced Epithelial to Mesenchymal Transition in Cancer. *Cancer Lett*2020, *487*, 10–20, doi:10.1016/J.CANLET.2020.05.012.

Hawiger, J. Innate Immunity and Inflammation: A Transcriptional Paradigm. *Immunol Res*2001, *23*, 99–109, doi:10.1385/IR:23:2-3:099.

Hu, C.J.; Sataur, A.; Wang, L.; Chen, H.; Simon, M.C. The N-Terminal Transactivation Domain Confers Target Gene Specificity of Hypoxia-Inducible Factors HIF-1alpha and HIF-2alpha. *Mol Biol Cell*2007, *18*, 4528–4542, doi:10.1091/MBC.E06-05-0419.

Humpton, T.J.; Vousden, K.H. Regulation of Cellular Metabolism and Hypoxia by P53. *Cold Spring Harb Perspect Med*2016, *6*, a026146, doi:10.1101/CSHPERSPECT.A026146.

Iliff, J.J.; Wang, M.; Zeppenfeld, D.M.; Venkataraman, A.; Plog, B.A.; Liao, Y.; Deane, R.; Nedergaard, M. Cerebral Arterial Pulsation Drives Paravascular CSF–Interstitial Fluid Exchange in the Murine Brain. *Journal of Neuroscience*2013, *33*, 18190–18199, doi:10.1523/JNEUROSCI.1592-13.2013.

Iliff, J.J.; Wang, M.; Zeppenfeld, D.M.; Venkataraman, A.; Plog, B.A.; Liao, Y.; Deane, R.; Nedergaard, M. Cerebral Arterial Pulsation Drives Paravascular CSF–Interstitial Fluid Exchange in the Murine Brain. *Journal of Neuroscience*2013, *33*, 18190–18199, doi:10.1523/JNEUROSCI.1592-13.2013.

Imray, C.; Chan, C.; Stubbings, A.; Rhodes, H.; Patey, S.; Wilson, M.H.; Bailey, D.M.; Wright, A.D. Time Course Variations in the Mechanisms by Which Cerebral Oxygen Delivery Is Maintained on Exposure to Hypoxia/Altitude. *High Alt Med Biol*2014, *15*, 21–27, doi:10.1089/HAM.2013.1079/ASSET/IMAGES/LARGE/FIGURE2.JPEG.

Imray, C.; Wright, A.; Subudhi, A.; Roach, R. Acute Mountain Sickness: Pathophysiology, Prevention, and Treatment. *Prog Cardiovasc Dis*2010, *52*, 467–484, doi:10.1016/J.PCAD.2010.02.003.

Imray, C.; Wright, A.; Subudhi, A.; Roach, R. Acute Mountain Sickness: Pathophysiology, Prevention, and Treatment. *Prog Cardiovasc Dis*2010, *52*, 467–484, doi:10.1016/J.PCAD.2010.02.003.

Jacovas, V.C.; Couto-Silva, C.M.; Nunes, K.; Lemes, R.B.; de Oliveira, M.Z.; Salzano, F.M.; Cátira Bortolini, M.; Hünemeier, T. Selection Scan Reveals Three New Loci Related to High Altitude Adaptation in Native Andeans OPEN., doi:10.1038/s41598-018-31100-6.

Jha, A.; Dheer, A.; Mehta, V.K.; Saha, S.K. Inter-Relational Dynamics of Various HR Aspects in High Altitude Illness Attrition. *https://services.igi-global.com/resolvedoi/resolve.aspx?doi=10.4018/978-1-7998-1566-2.ch006*1AD, 114–132, doi:10.4018/978-1-7998-1566-2.CH006.

Jha, R.M.; Kochanek, P.M.; Simard, J.M. Pathophysiology and Treatment of Cerebral Edema in Traumatic Brain Injury. *Neuropharmacology*2019, *145*, 230–246, doi:10.1016/J.NEUROPHARM.2018.08.004.

Johnson, T.S.; Rock, P.B. Acute Mountain Sickness. *http://dx.doi.org/10.1056/NEJM198809293191306*2010, *319*, 841–845, doi:10.1056/NEJM198809293191306.

Julian, C.G.; Moore, L.G. Human Genetic Adaptation to High Altitude: Evidence from the Andes. *Genes 2019, Vol. 10, Page 150*2019, *10*, 150, doi:10.3390/GENES10020150.

Kabel, A.M.; al Thumali, A.M.; Aldowiala, K.A.; Habib, R.D.; Aljuaid, S.S.; Alharthi, H.A. Sleep Disorders in Adolescents and Young Adults: Insights into Types, Relationship to Obesity and High Altitude and Possible Lines of Management. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*2018, *12*, 777–781, doi:10.1016/J.DSX.2018.04.029.

Kaelin, W.G. ROS: Really Involved in Oxygen Sensing. *Cell Metab*2005, *1*, 357–358, doi:10.1016/J.CMET.2005.05.006.

Karagiannidis, C.; Hense, G.; Rueckert, B.; Mantel, P.Y.; Ichters, B.; Blaser, K.; Menz, G.; Schmidt-Weber, C.B. High-Altitude Climate Therapy Reduces Local Airway Inflammation and Modulates Lymphocyte Activation. *Scand J Immunol*2006, *63*, 304–310, doi:10.1111/J.1365-3083.2006.01739.X.

Kastenhuber, E.R.; Lowe, S.W. Putting P53 in Context. *Cell*2017, *170*, 1062–1078, doi:10.1016/J.CELL.2017.08.028.

Keith, B.; Johnson, R.S.; Simon, M.C. HIF1α and HIF2α: Sibling Rivalry in Hypoxic Tumour Growth and Progression. *Nature Reviews Cancer 2011 12:1*2011, *12*, 9–22, doi:10.1038/nrc3183.

Khan, S.Z.; Ajmal, N.; Shaikh, R. Diabetic Retinopathy and Vascular Endothelial Growth Factor Gene Insertion/Deletion Polymorphism. *Can J Diabetes*2020, *44*, 287–291, doi:10.1016/J.JCJD.2019.08.005.

Khanna, K.; Mishra, K.P.; Ganju, L.; Kumar, B.; Singh, S.B. High-Altitude-Induced Alterations in Gut-Immune Axis: A Review. *https://doi.org/10.1080/08830185.2017.1407763*2017, *37*, 119–126, doi:10.1080/08830185.2017.1407763.

Khanna, K.; Mishra, K.P.; Ganju, L.; Kumar, B.; Singh, S.B. High-Altitude-Induced Alterations in Gut-Immune Axis: A Review. *Int Rev Immunol*2018, *37*, 119–126, doi:10.1080/08830185.2017.1407763.

Khodaee, M.; Grothe, H.L.; Seyfert, J.H.; VanBaak, K. Athletes at High Altitude. *Sports Health*2016, *8*, 126–132, doi:10.1177/1941738116630948.

Kiesewetter, B.; Raderer, M. Immunomodulatory Treatment for Mucosa-Associated Lymphoid Tissue

Lymphoma (MALT Lymphoma). *Hematol Oncol*2020, *38*, 417–424, doi:10.1002/HON.2754.

Kodama, T.; Takehara, T.; Hikita, H.; Shimizu, S.; Shigekawa, M.; Tsunematsu, H.; Li, W.; Miyagi, T.; Hosui, A.; Tatsumi, T.; et al. Increases in P53 Expression Induce CTGF Synthesis by Mouse and Human Hepatocytes and Result in Liver Fibrosis in Mice. *J Clin Invest*2011, *121*, 3343–3356, doi:10.1172/JCI44957.

Konac, E.; Onen, H.I.; Metindir, J.; Alp, E.; Biri, A.A.; Ekmekci, A. An Investigation of Relationships between Hypoxia-Inducible Factor-1α Gene Polymorphisms and Ovarian, Cervical and Endometrial Cancers. *Cancer Detect Prev*2007, *31*, 102–109, doi:10.1016/J.CDP.2007.01.001.

Koumenis, C.; Alarcon, R.; Hammond, E.; Sutphin, P.; Hoffman, W.; Murphy, M.; Derr, J.; Taya, Y.; Lowe, S.W.; Kastan, M.; et al. Regulation of P53 by Hypoxia: Dissociation of Transcriptional Repression and Apoptosis from P53-Dependent Transactivation. *Mol Cell Biol*2001, *21*, 1297–1310, doi:10.1128/MCB.21.4.1297-1310.2001.

Kumar, B.; Singh, S.B. Effect of Intermittent Normobaric Hypoxia Exposures on Acute Mountain Sickness During Acute Ascent to 3500 m in Indian Military Personnel., doi:10.14429/dlsj.3.12906.

Langerød, A.; Zhao, H.; Borgan, Ø.; Nesland, J.M.; Bukholm, I.R.K.; Ikdahl, T.; Kåresen, R.; Børresen-Dale, A.L.; Jeffrey, S.S. TP53 Mutation Status and Gene Expression Profiles Are Powerful Prognostic Markers of Breast Cancer. *Breast Cancer Res*2007, *9*, doi:10.1186/BCR1675.

Larson, E.B.; Roach, R.C.; Schoene, R.B.; Hornbein, T.F. Acute Mountain Sickness and Acetazolamide: Clinical Efficacy and Effect on Ventilation. *JAMA*1982, *248*, 328–332, doi:10.1001/JAMA.1982.03330030034021.

Latif, F.; Tory, K.; Gnarra, J.; Yao, M.; Duh, F.M.; Orcutt, M. lou; Stackhouse, T.; Kuzmin, I.; Modi, W.; Geil, L.; et al. Identification of the von Hippel-Lindau Disease Tumor Suppressor Gene. *Science*1993, *260*, 1317–1320, doi:10.1126/SCIENCE.8493574.

Lawley, J.S.; Alperin, N.; Bagci, A.M.; Lee, S.H.; Mullins, P.G.; Oliver, S.J.; Macdonald, J.H. Normobaric Hypoxia and Symptoms of Acute Mountain Sickness: Elevated Brain Volume and Intracranial Hypertension. *Ann Neurol*2014, *75*, 890–898, doi:10.1002/ANA.24171.

Lee, H.; Xie, L.; Yu, M.; Kang, H.; Feng, T.; Deane, R.; Logan, J.; Nedergaard, M.; Benveniste, H. The Effect of Body Posture on Brain Glymphatic Transport. *Journal of Neuroscience*2015, *35*, 11034–11044, doi:10.1523/JNEUROSCI.1625-15.2015.

Lee, S.H.; Jee, J.G.; Bae, J.S.; Liu, K.H.; Lee, Y.M. A Group of Novel HIF-1α Inhibitors, Glyceollins, Blocks HIF-1α Synthesis and Decreases Its Stability via Inhibition of the PI3K/AKT/MTOR Pathway and Hsp90 Binding. *J Cell Physiol*2015, *230*, 853–862, doi:10.1002/JCP.24813.

Leigh, T.; Scalia, R.G.; Autieri, M. v. Resolution of Inflammation in Immune and Nonimmune Cells by Interleukin-19. *Am J Physiol Cell Physiol*2020, *319*, C457–C464, doi:10.1152/AJPCELL.00247.2020/ASSET/IMAGES/LARGE/ZH00092087770003.JPEG.

León-Velarde, F.; Maggiorini, M.; Reeves, J.T.; Aldashev, A.; Asmus, I.; Bernardi, L.; Ge, R.L.; Hackett, P.; Kobayashi, T.; Moore, L.G.; et al. Consensus Statement on Chronic and Subacute High Altitude Diseases. *High Alt Med Biol*2005, *6*, 147–157, doi:10.1089/HAM.2005.6.147.

Li, D.; Zhang, L.; Huang, X.; Liu, L.; He, Y.; Xu, L.; Zhang, Y.; Zhao, T.; Wu, L.; Zhao, Y.; et al. WIP1 Phosphatase Plays a Critical Neuroprotective Role in Brain Injury Induced by High-Altitude Hypoxic Inflammation. *Neurosci Bull*2017, *33*, 292–298, doi:10.1007/S12264-016-0095-9/FIGURES/4.

Li, F.P.; Fraumeni, J.F. Soft-Tissue Sarcomas, Breast Cancer, and Other Neoplasms. A Familial Syndrome? *Ann Intern Med*1969, *71*, 747–752, doi:10.7326/0003-4819-71-4-747.

Li, K.; Gesang, L.; Dan, Z.; Gusang, L. Genome-Wide Transcriptional Analysis Reveals the Protection against Hypoxia-Induced Oxidative Injury in the Intestine of Tibetans via the Inhibition of GRB2/EGFR/PTPN11 Pathways. *Oxid Med Cell Longev*2016, *2016*, doi:10.1155/2016/6967396.

Li, L.; Zhao, X. Comparative Analyses of Fecal Microbiota in Tibetan and Chinese Han Living at Low or High Altitude by Barcoded 454 Pyrosequencing. *Scientific Reports 2015 5:1*2015, *5*, 1–10, doi:10.1038/srep14682.

Li, Y.; Zhang, Y.; Zhang, Y. Research Advances in Pathogenesis and Prophylactic Measures of Acute High Altitude Illness. *Respir Med*2018, *145*, 145–152, doi:10.1016/J.RMED.2018.11.004.

Liang, D.; Bhatta, S.; Gerzanich, V.; Simard, J.M. Cytotoxic Edema: Mechanisms of Pathological Cell Swelling. *Neurosurg Focus*2007, *22*, 1–9, doi:10.3171/FOC.2007.22.5.3.

Liang, J.; Zhang, Z.; Liang, L.; Shen, Y.; Ouyang, K. HIF-1α Regulated Tongue Squamous Cell Carcinoma Cell Growth via Regulating VEGF Expression in a Xenograft Model. *Ann Transl Med*2014, *2*, doi:10.3978/J.ISSN.2305-5839.2014.08.01.

Lin, S.; Wu, H.; Wang, C.; Xiao, Z.; Xu, F. Regulatory T Cells and Acute Lung Injury: Cytokines, Uncontrolled Inflammation, and Therapeutic Implications. *Front Immunol*2018, *9*, 1545, doi:10.3389/FIMMU.2018.01545/BIBTEX.

Liu, Y.; Cox, S.R.; Morita, T.; Kourembanas, S. Hypoxia Regulates Vascular Endothelial Growth Factor Gene Expression in Endothelial Cells. Identification of a 5' Enhancer. *Circ Res*1995, *77*, 638–643,

doi:10.1161/01.RES.77.3.638.

Liu, Y.; Qiao, J.T.; Yuan, X.Z.; Guo, R.B.; Qiu, Y.L. Hydrogenispora Ethanolica Gen. Nov., Sp. Nov., an Anaerobic Carbohydrate-Fermenting Bacterium from Anaerobic Sludge. *Int J Syst Evol Microbiol*2014, *64*, 1756–1762, doi:10.1099/IJS.0.060186-0/CITE/REFWORKS.

Loboda, A.; Jozkowicz, A.; Dulak, J. HIF-1 versus HIF-2--Is One More Important than the Other? *Vascul Pharmacol*2012, *56*, 245–251, doi:10.1016/J.VPH.2012.02.006.

Loughery, J.; Cox, M.; Smith, L.M.; Meek, D.W. NAR Breakthrough Article Critical Role for P53-Serine 15 Phosphorylation in Stimulating Transactivation at P53-Responsive Promoters. *Nucleic Acids Res*2014, *42*, 7666–7680, doi:10.1093/nar/gku501.

Luks, A.M.; Swenson, E.R. Evaluating the Risks of High Altitude Travel in Chronic Liver Disease Patients. *https://home.liebertpub.com/ham*2015, *16*, 80–88, doi:10.1089/HAM.2014.1122.

Luks, A.M.; Swenson, E.R.; Bärtsch, P. Acute High-Altitude Sickness. *European Respiratory Review*2017, *26*, doi:10.1183/16000617.0096-2016.

MacInnis, M.J.; Koehle, M.S. Evidence for and Against Genetic Predispositions to Acute and Chronic Altitude Illnesses. *High Alt Med Biol*2016, *17*, 281–293, doi:10.1089/HAM.2016.0024.

MacInnis, M.J.; Koehle, M.S.; Rupert, J.L. Evidence for a Genetic Basis for Altitude Illness: 2010 Update. *https://home.liebertpub.com/ham*2010, *11*, 349–368, doi:10.1089/HAM.2010.1030.

MacInnis, M.J.; Wang, P.; Koehle, M.S.; Rupert, J.L. The Genetics of Altitude Tolerance: The Evidence for Inherited Susceptibility to Acute Mountain Sickness. *J Occup Environ Med*2011, *53*, 159–168, doi:10.1097/JOM.0B013E318206B112.

Makino, Y.; Nakamura, H.; Ikeda, E.; Ohnuma, K.; Yamauchi, K.; Yabe, Y.; Poellinger, L.; Okada, Y.; Morimoto, C.; Tanaka, H. Hypoxia-Inducible Factor Regulates Survival of Antigen Receptor-Driven T Cells. *The Journal of Immunology*2003, *171*, 6534–6540, doi:10.4049/JIMMUNOL.171.12.6534.

Marhold, M.; Tomasich, E.; El-Gazzar, A.; Heller, G.; Spittler, A.; Horvat, R.; Krainer, M.; Horak, P. HIF1α Regulates MTOR Signaling and Viability of Prostate Cancer Stem Cells. *Mol Cancer Res*2015, *13*, 556–564, doi:10.1158/1541-7786.MCR-14-0153-T.

Meehan, R.T.; Zavala, D.C. The Pathophysiology of Acute High-Altitude Illness. *Am J Med*1982, *73*, 395–403, doi:10.1016/0002-9343(82)90733-1.

Mirrakhimov, A.E.; Strohl, K.P. High-Altitude Pulmonary Hypertension: An Update on Disease Pathogenesis and Management. *Open Cardiovasc Med J*2016, *10*, 19, doi:10.2174/1874192401610010019.

Mirrakhimov, A.E.; Strohl, K.P. High-Altitude Pulmonary Hypertension: An Update on Disease Pathogenesis and Management. *Open Cardiovasc Med J*2016, *10*, 19, doi:10.2174/1874192401610010019.

Naseribafrouei, A.; Hestad, K.; Avershina, E.; Sekelja, M.; Linløkken, A.; Wilson, R.; Rudi, K. Correlation between the Human Fecal Microbiota and Depression. *Neurogastroenterology & Motility*2014, *26*, 1155–1162, doi:10.1111/NMO.12378.

Newman, J.H.; Holt, T.N.; Cogan, J.D.; Womack, B.; Phillips, J.A.; Li, C.; Kendall, Z.; Stenmark, K.R.; Thomas, M.G.; Brown, R.D.; et al. Increased Prevalence of EPAS1 Variant in Cattle with High-Altitude Pulmonary Hypertension. *Nature Communications 2015 6:1*2015, *6*, 1–5, doi:10.1038/ncomms7863.

Nieto Estrada, V.H.; Molano Franco, D.; Medina, R.D.; Gonzalez Garay, A.G.; Martí-Carvajal, A.J.; Arevalo-Rodriguez, I. Interventions for Preventing High Altitude Illness: Part 1. Commonly-Used Classes of Drugs. *Cochrane Database Syst Rev*2017, *6*, doi:10.1002/14651858.CD009761.PUB2.

Nussbaumer-Ochsner, Y.; Ursprung, J.; Siebenmann, C.; Maggiorini, M.; Bloch, K.E. Effect of Short-Term Acclimatization to High Altitude on Sleep and Nocturnal Breathing. *Sleep*2012, *35*, 419–423, doi:10.5665/SLEEP.1708.

Oswald-Mammosser, M.; Weitzenblum, E.; Quoix, E.; Moser, G.; Chaouat, A.; Charpentier, C.; Kessler, R. Prognostic Factors in COPD Patients Receiving Long-Term Oxygen Therapy: Importance of Pulmonary Artery Pressure. *Chest*1995, *107*, 1193–1198, doi:10.1378/CHEST.107.5.1193.

Palazon, A.; Goldrath, A.W.; Nizet, V.; Johnson, R.S. HIF Transcription Factors, Inflammation, and Immunity. *Immunity*2014, *41*, 518–528, doi:10.1016/J.IMMUNI.2014.09.008.

Pham, K.; Parikh, K.; Heinrich, E.C. Hypoxia and Inflammation: Insights From High-Altitude Physiology. *Front Physiol*2021, *12*, 712, doi:10.3389/FPHYS.2021.676782/BIBTEX.

Pla, R.; Brocherie, F.; le Garrec, S.; Richalet, J.P. Effectiveness of the Hypoxic Exercise Test to Predict Altitude Illness and Performance at Moderate Altitude in High-Level Swimmers. *Physiol Rep*2020, *8*, e14390, doi:10.14814/PHY2.14390.

Power, S.E.; O'Toole, P.W.; Stanton, C.; Ross, R.P.; Fitzgerald, G.F. Intestinal Microbiota, Diet and Health. *Br J Nutr*2014, *111*, 387–402, doi:10.1017/S0007114513002560.

Pullamsetti, S.S.; Mamazhakypov, A.; Weissmann, N.; Seeger, W.; Savai, R. Hypoxia-Inducible Factor Signaling in Pulmonary Hypertension. *J Clin Invest*2020, *130*, 5638–5651, doi:10.1172/JCI137558.

Ramsoe, K.; Jarnum, S.; Preisig, R.; Tauber, J.; Tygstrup, N.; Westergaard, H. Liver Function and Blood Flow at High Altitude. *https://doi.org/10.1152/jappl.1970.28.6.725*1970, *28*, 725–727, doi:10.1152/JAPPL.1970.28.6.725.

Recalde, S.; Alargunsoro, L.; Sáez, V.J.; Garcia-Garcia, L.; Milagro, F.I.; Ibañez, R.; Villegas, A.; Cires, M. Risk and Protective Factors for Acute Mountain Sickness: A Meta-Analysis Title: Risk and Protective Factors for Acute Mountain Sickness: A Meta-Analysis. 2021, doi:10.21203/rs.3.rs-812272/v1.

Ren, H.; Luo, J.Q.; Gao, Y.C.; Chen, M.Y.; Chen, X.P.; Zhou, H.H.; Jiang, Y.; Zhang, W. Genetic Association of Hypoxia Inducible Factor 1-Alpha (HIF1A) Pro582Ser Polymorphism with Risk of Diabetes and Diabetic Complications. *Aging (Albany NY)*2020, *12*, 12783, doi:10.18632/AGING.103213.

Richards, P. High Altitude Illness. *Article in Journal of the Royal Army Medical Corps*2011, doi:10.1136/jramc-151-04-05.

Roach, R.C.; Hackett, P.H.; Oelz, O.; Bärtsch, P.; Luks, A.M.; MacInnis, M.J.; Baillie, J.K.; Achatz, E.; Albert, E.; Zafren, K.; et al. The 2018 Lake Louise Acute Mountain Sickness Score. *High Alt Med Biol*2018, *19*, 4, doi:10.1089/HAM.2017.0164.

Roach, R.C.; Houston, C.S.; Honigman, B.; Nicholas, R.A.; Yaron, M.; Grissom, C.K.; Alexander, J.K.; Hultgren, H.N. How Well Do Older Persons Tolerate Moderate Altitude? *Western Journal of Medicine*1995, *162*, 32.

Robertson, M.J. Evaluation of the Immunological Effects of Cytokines Administered to Patients With Cancer. 2007, 297–317, doi:10.1007/978-1-59745-350-9_15.

Robinson, S.; King, A.; medicine, V.A.-A.; 1971, undefined Acute Mountain Sickness: Reproducibility of Its Severity and Duration in an Individual. *pubmed.ncbi.nlm.nih.gov*.

Royds, J.A.; Dower, S.K.; Qwarnstrom, E.E.; Lewis, C.E. Response of Tumour Cells to Hypoxia: Role of P53 and NFkB. *Molecular Pathology*1998, *51*, 55, doi:10.1136/MP.51.2.55.

Sampson, J.B.; Cymerman, A.; Burse, R.L.; Maher, J.T.; Rock, P.B. Procedures for the Measurement of Acute Mountain Sickness. *Aviat Space Environ Med*1983, *54*, 1063–1073.

San, T.; Polat, S.; Cingi, C.; Eskiizmir, G.; Oghan, F.; Cakir, B. Effects of High Altitude on Sleep and Respiratory System and Theirs Adaptations. *The Scientific World Journal*2013, *2013*, doi:10.1155/2013/241569.

Schneider, M.; Bernasch, D.; Weymann, J.; Holle, R.; Bärtsch, P. Acute Mountain Sickness: Influence of Susceptibility, Preexposure, and Ascent Rate. *Med Sci Sports Exerc*2002, *34*, 1886–1891, doi:10.1097/00005768-200212000-00005.

Schoch, H.J.; Fischer, S.; Marti, H.H. Hypoxia-induced Vascular Endothelial Growth Factor Expression Causes Vascular Leakage in the Brain. *Brain*2002, *125*, 2549–2557, doi:10.1093/BRAIN/AWF257.

Schommer, K.; Kallenberg, K.; Lutz, K.; Bärtsch, P.; Knauth, M. Hemosiderin Deposition in the Brain as Footprint of High-Altitude Cerebral Edema. *Neurology*2013, *81*, 1776–1779, doi:10.1212/01.WNL.0000435563.84986.78.

Scoggin, C.H.; Hyers, T.M.; Reeves, J.T.; Grover, R.F. High-Altitude Pulmonary Edema in the Children and Young Adults of Leadville, Colorado. *http://dx.doi.org/10.1056/NEJM197712082972309*20 10, *297*, 1269–1272, doi:10.1056/NEJM197712082972309.

Scortegagna, M.; Ding, K.; Zhang, Q.; Oktay, Y.; Bennett, M.J.; Bennett, M.; Shelton, J.M.; Richardson, J.A.; Moe, O.; Garcia, J.A. HIF-2alpha Regulates Murine Hematopoietic Development in an Erythropoietin-Dependent Manner. *Blood*2005, *105*, 3133–3140, doi:10.1182/BLOOD-2004-05-1695.

Shen, Y.; Zhang, J.; Yang, J.; Liu, C.; Bian, S.; Zhang, C.; Yu, J.; Gao, X.; Huang, L. Association of EPAS1 and PPARA Gene Polymorphisms with High-Altitude Headache in Chinese Han Population. 2020, doi:10.1155/2020/1593068.

Shi, L.Z.; Wang, R.; Huang, G.; Vogel, P.; Neale, G.; Green, D.R.; Chi, H. HIF1alpha-Dependent Glycolytic Pathway Orchestrates a Metabolic Checkpoint for the Differentiation of TH17 and Treg Cells. *J Exp Med*2011, *208*, 1367–1376, doi:10.1084/JEM.20110278.

Shimoda, L.A.; Laurie, S.S. HIF and Pulmonary Vascular Responses to Hypoxia. *J Appl Physiol (1985)*2014, *116*, 867–874, doi:10.1152/JAPPLPHYSIOL.00643.2013.

Silber, E.; Sonnenberg, P.; Collier, D.J.; Pollard, A.J.; Murdoch, D.R.; Goadsby, P.J. Clinical Features of Headache at Altitude: A Prospective Study. *Neurology*2003, *60*, 1167–1171, doi:10.1212/01.WNL.0000055876.26737.B9.

Simonneau, G.; Montani, D.; Celermajer, D.S.; Denton, C.P.; Gatzoulis, M.A.; Krowka, M.; Williams, P.G.; Souza, R. Haemodynamic Definitions and Updated Clinical Classification of Pulmonary Hypertension., doi:10.1183/13993003.01913-2018.

Simonneau, G.; Robbins, I.M.; Beghetti, M.; Channick, R.N.; Delcroix, M.; Denton, C.P.; Elliott, C.G.; Gaine, S.P.; Gladwin, M.T.; Jing, Z.C.; et al. Updated Clinical Classification of Pulmonary Hypertension. *J Am Coll Cardiol*2009, *54*, S43–S54, doi:10.1016/J.JACC.2009.04.012.

Simonson, T.S.; McClain, D.A.; Jorde, L.B.; Prchal, J.T. Genetic Determinants of Tibetan High-Altitude Adaptation. *Hum Genet*2012, *131*, 527–533, doi:10.1007/S00439-011-1109-3/FIGURES/1.

Simonson, T.S.; Yang, Y.; Huff, C.D.; Yun, H.; Qin, G.; Witherspoon, D.J.; Bai, Z.; Lorenzo, F.R.; Xing, J.; Jorde, L.B.; et al. Genetic Evidence for High-Altitude Adaptation in Tibet. *Science*2010, *329*, 72–75, doi:10.1126/SCIENCE.1189406.

Sitkovsky, M. v.; Lukashev, D.; Apasov, S.; Kojima, H.; Koshiba, M.; Caldwell, C.; Ohta, A.; Thiel, M. Physiological Control of Immune Response and

Inflammatory Tissue Damage by Hypoxia-Inducible Factors and Adenosine A2A Receptors. *Annu Rev Immunol*2004, *22*, 657–682, doi:10.1146/ANNUREV.IMMUNOL.22.012703.104731.

Small, E.; Phillips, C.; Marvel, J.; Lipman, G. Older Age as a Predictive Risk Factor for Acute Mountain Sickness. *Am J Med*2022, *135*, 386-392.e1, doi:10.1016/J.AMJMED.2021.10.003.

Sobin, S.S.; Tremer, H.M.; Hardy, J.D.; Chiodi, H.P. Changes in Arteriole in Acute and Chronic Hypoxic Pulmonary Hypertension and Recovery in Rat. *J Appl Physiol Respir Environ Exerc Physiol*1983, *55*, 1445–1455, doi:10.1152/JAPPL.1983.55.5.1445.

Song, Y.; Hu, J.; Chen, Q.; Guo, J.; Zou, Y.; Zhang, W.; Chen, X.; Hu, W.; Huang, P. Association between Vascular Endothelial Growth Factor Rs699947 Polymorphism and the Risk of Three Major Urologic Neoplasms (Bladder Cancer, Prostate Cancer, and Renal Cell Carcinoma): A Meta-Analysis Involving 11,204 Subjects. *Gene*2018, *679*, 241–252, doi:10.1016/J.GENE.2018.09.005.

Stickle, N.H.; Chung, J.; Klco, J.M.; Hill, R.P.; Kaelin, W.G.; Ohh, M. PVHL Modification by NEDD8 Is Required for Fibronectin Matrix Assembly and Suppression of Tumor Development. *Mol Cell Biol*2004, *24*, 3251–3261, doi:10.1128/MCB.24.8.3251-3261.2004.

Stokum, J.A.; Gerzanich, V.; Simard, J.M. Molecular Pathophysiology of Cerebral Edema. *Journal of Cerebral Blood Flow and Metabolism*2016, *36*, 513–538, doi:10.1177/0271678X15617172.

Storz, J.F. High-Altitude Adaptation: Mechanistic Insights from Integrated Genomics and Physiology. *Mol Biol Evol*2021, *38*, 2677–2691, doi:10.1093/MOLBEV/MSAB064.

Tan, Q.; Kerestes, H.; Percy, M.J.; Pietrofesa, R.; Chen, L.; Khurana, T.S.; Christofidou-Solomidou, M.; Lappin, T.R.J.; Lee, F.S. Erythrocytosis and Pulmonary Hypertension in a Mouse Model of Human HIF2A Gain of Function Mutation. *J Biol Chem*2013, *288*, 17134, doi:10.1074/JBC.M112.444059.

Tan, Q.; Kerestes, H.; Percy, M.J.; Pietrofesa, R.; Chen, L.; Khurana, T.S.; Christofidou-Solomidou, M.; Lappin, T.R.J.; Lee, F.S. Erythrocytosis and Pulmonary Hypertension in a Mouse Model of Human HIF2A Gain of Function Mutation. *J Biol Chem*2013, *288*, 17134, doi:10.1074/JBC.M112.444059.

Taylor, A. High-Altitude Illnesses: Physiology, Risk Factors, Prevention, and Treatment. *Rambam Maimonides Med J*2011, *2*, doi:10.5041/RMMJ.10022.

Tiollier, E.; Schmitt, A.L.; Burnat, A.P.; Fouillot, A.J.-P.; Robach, P.; Filaire, A.E.; Guezennec, A.C.; Richalet, A.J.-P. Living High-Training Low Altitude Training: Effects on Mucosal Immunity., doi:10.1007/s00421-005-1317-4.

Tuder, R.M.; Flook, B.E.; Voelkel, N.F. Increased Gene Expression for VEGF and the VEGF Receptors KDR/Flk and Flt in Lungs Exposed to Acute or to Chronic Hypoxia. Modulation of Gene Expression by Nitric Oxide. *J Clin Invest*1995, *95*, 1798–1807, doi:10.1172/JCI117858.

Turner, R.E.F.; Gatterer, H.; Falla, M.; Lawley, J.S. High-Altitude Cerebral Edema: Its Own Entity or End-Stage Acute Mountain Sickness? *J Appl Physiol*2021, *131*, 313–325, doi:10.1152/JAPPLPHYSIOL.00861.2019/ASSET/IMAGES/LARGE/JAPPLPHYSIOL.00861.2019_F003.JPEG.

Ucrós, S.; Granados, C.M.; Castro-Rodríguez, J.A.; Hill, C.M. Oxygen Saturation in Childhood at High Altitude: A Systematic Review. *High Alt Med Biol*2020, *21*, 114–125, doi:10.1089/HAM.2019.0077/ASSET/IMAGES/LARGE/HAM.2019.0077_FIGURE7.JPEG.

van de Pol, J.A.A.; van den Brandt, P.A.; van Engeland, M.; Godschalk, R.W.L.; van Schooten, F.J.; Hogervorst, J.G.F.; Schouten, L.J. Germline Polymorphisms in the Von Hippel-Lindau and Hypoxia-Inducible Factor 1-Alpha Genes, Gene-Environment and Gene-Gene Interactions and Renal Cell Cancer. *Scientific Reports 2020 10:1*2020, *10*, 1–9, doi:10.1038/s41598-019-56980-0.

Verbiest, A.; Lambrechts, D.; van Brussel, T.; Couchy, G.; Wozniak, A.; Méjean, A.; Lerut, E.; Oudard, S.; Verkarre, V.; Job, S.; et al. Polymorphisms in the Von Hippel–Lindau Gene Are Associated With Overall Survival in Metastatic Clear-Cell Renal-Cell Carcinoma Patients Treated With VEGFR Tyrosine Kinase Inhibitors. *Clin Genitourin Cancer*2018, *16*, 266–273, doi:10.1016/J.CLGC.2018.01.013.

Villafuerte, F.C.; Corante, N. Chronic Mountain Sickness: Clinical Aspects, Etiology, Management, and Treatment. *High Alt Med Biol*2016, *17*, 61, doi:10.1089/HAM.2016.0031.

Villca, N.; Asturizaga, A.; Heath-Freudenthal, A. High-Altitude Illnesses and Air Travel: Pediatric Considerations. *Pediatric Clinics*2021, *68*, 305–319, doi:10.1016/J.PCL.2020.09.015.

Vogelstein, B.; Lane, D.; Levine, A.J. Surfing the P53 Network. *Nature 2000 408:6810*2000, *408*, 307–310, doi:10.1038/35042675.

Voskarides, K. Combination of 247 Genome-Wide Association Studies Reveals High Cancer Risk as a Result of Evolutionary Adaptation. *Mol Biol Evol*2018, *35*, 473–485, doi:10.1093/MOLBEV/MSX305.

Vousden, K.H.; Prives, C. Blinded by the Light: The Growing Complexity of P53. *Cell*2009, *137*, 413–431, doi:10.1016/J.CELL.2009.04.037.

Walmsley, S.R.; Print, C.; Farahi, N.; Peyssonnaux, C.; Johnson, R.S.; Cramer, T.; Sobolewski, A.; Condliffe,

A.M.; Cowburn, A.S.; Johnson, N.; et al. Hypoxia-Induced Neutrophil Survival Is Mediated by HIF-1α–Dependent NF-KB Activity. *Journal of Experimental Medicine*2005, *201*, 105–115, doi:10.1084/JEM.20040624.

Wang, B.; Zhang, Y.B.; Zhang, F.; Lin, H.; Wang, X.; Wan, N.; Ye, Z.; Weng, H.; Zhang, L.; Li, X.; et al. On the Origin of Tibetans and Their Genetic Basis in Adapting High-Altitude Environments. *PLoS One*2011, *6*, doi:10.1371/JOURNAL.PONE.0017002.

Wang, V.; Davis, D.A.; Haque, M.; Huang, L.E.; Yarchoan, R. Differential Gene Up-Regulation by Hypoxia-Inducible Factor-1alpha and Hypoxia-Inducible Factor-2alpha in HEK293T Cells. *Cancer Res*2005, *65*, 3299–3306, doi:10.1158/0008-5472.CAN-04-4130.

Weil, J. v. Sleep at High Altitude. *https://home.liebertpub.com/ham*2004, *5*, 180–189, doi:10.1089/1527029041352162.

Wijaya, A.R.; Surudarma, I.W.; Wihandani, D.M.; Ardyan Sudharta Putra, I.W. Polymorphisms of Vascular Endothelial Growth Factor—2578C/A Rs699947 Are Risk Factors for Diabetic Retinopathy in Type-2 Diabetes Mellitus Patients in Bali, Indonesia. *Biomedicine (Taipei)*2021, *11*, 11, doi:10.37796/2211-8039.1170.

Willie, C.K.; Smith, K.J.; Day, T.A.; Ray, L.A.; Lewis, N.C.S.; Bakker, A.; MacLeod, D.B.; Ainslie, P.N. Regional Cerebral Blood Flow in Humans at High Altitude: Gradual Ascent and 2 Wk at 5,050 m. *J Appl Physiol*2014, *116*, 905–910, doi:10.1152/JAPPLPHYSIOL.00594.2013/ASSET/IMAGES/LARGE/ZDG0201307520003.JPEG.

Wilson, M.H.; Edsell, M.E.G.; Davagnanam, I.; Hirani, S.P.; Martin, D.S.; Levett, D.Z.H.; Thornton, J.S.; Golay, X.; Strycharczuk, L.; Newman, S.P.; et al. Cerebral Artery Dilatation Maintains Cerebral Oxygenation at Extreme Altitude and in Acute Hypoxiaan Ultrasound and MRI Study. *Journal of Cerebral Blood Flow and Metabolism*2011, *31*, 2019–2029, doi:10.1038/jcbfm.2011.81.

Witt, K.E.; Huerta-Sánchez, E. Convergent Evolution in Human and Domesticate Adaptation to High-Altitude Environments. *Philosophical Transactions of the Royal Society B*2019, *374*, doi:10.1098/RSTB.2018.0235.

Wolfel, E.E.; Selland, M.A.; Mazzeo, R.S.; Reeves, J.T. Systemic Hypertension at 4,300 m Is Related to Sympathoadrenal Activity. *https://doi.org/10.1152/jappl.1994.76.4.1643*1994, *76*, 1643–1650, doi:10.1152/JAPPL.1994.76.4.1643.

Woods, P.; Alcock, J. High Altitude Pulmonary Edema. *Evol Med Public Health*2021, *9*, 118–119, doi:10.1093/emph/eoaa052.

Wu, T.; Zhang, Z.-T.; Li, L.; Liu, R.-Y.; Bei, B.-T. Correlation between Hypoxia-Inducible Factor-1α C1772T/G1790A Polymorphisms and Head and Neck Cancer Risk: A Meta-Analysis., doi:10.1186/s12957-021-02324-0.

Xie, H.; Lv, J.; Ji, Y.; Du, X.; Yang, X. Primary Hepatic Mucosa-Associated Lymphoid Tissue Lymphoma: A Case Report and Literature Review. *Medicine*2019, *98*, doi:10.1097/MD.0000000000015034.

Xie, L.; Kang, H.; Xu, Q.; Chen, M.J.; Liao, Y.; Thiyagarajan, M.; O'Donnell, J.; Christensen, D.J.; Nicholson, C.; Iliff, J.J.; et al. Sleep Drives Metabolite Clearance from the Adult Brain. *Science (1979)*2013, *342*, 373–377, doi:10.1126/SCIENCE.1241224/SUPPL_FILE/XIE-SM.PDF.

Xu, S.; Li, S.; Yang, Y.; Tan, J.; Lou, H.; Jin, W.; Yang, L.; Pan, X.; Wang, J.; Shen, Y.; et al. A Genome-Wide Search for Signals of High-Altitude Adaptation in Tibetans. *Mol Biol Evol*2011, *28*, 1003–1011, doi:10.1093/MOLBEV/MSQ277.

Young, T.K.; Kelly, J.J.; Friborg, J.; Soininen, L.; Wong, K.O. Cancer among Circumpolar Populations: An Emerging Public Health Concern. *https://doi.org/10.3402/ijch.v75.29787*2016, *75*, 29787, doi:10.3402/IJCH.V75.29787.

Zafren, K. Prevention of High Altitude Illness. *Travel Med Infect Dis*2014, *12*, 29–39, doi:10.1016/J.TMAID.2013.12.002.

Zhang, F.; Wu, W.; Deng, Z.; Zheng, X.; Zhang, J.; Deng, S.; Chen, J.; Ma, Q.; Wang, Y.; Yu, X.; et al. High Altitude Increases the Expression of Hypoxia-Inducible Factor 1α and Inducible Nitric Oxide Synthase with Intest-Inal Mucosal Barrier Failure in Rats. *Int J Clin Exp Pathol*2015, *8*, 5189.

Zhang, F.; Wu, W.; Deng, Z.; Zheng, X.; Zhang, J.; Deng, S.; Chen, J.; Ma, Q.; Wang, Y.; Yu, X.; et al. High Altitude Increases the Expression of Hypoxia-Inducible Factor 1α and Inducible Nitric Oxide Synthase with Intest-Inal Mucosal Barrier Failure in Rats. *Int J Clin Exp Pathol*2015, *8*, 5189.

Zhang, J.; Zhang, Q. VHL and Hypoxia Signaling: Beyond HIF in Cancer. *Biomedicines*2018, *6*, doi:10.3390/BIOMEDICINES6010035.

Zhang, W.; Jiao, L.; Liu, R.; Zhang, Y.; Ji, Q.; Zhang, H.; Gao, X.; Ma, Y.; Shi, H.N. The Effect of Exposure to High Altitude and Low Oxygen on Intestinal Microbial Communities in Mice. *PLoS One*2018, *13*, e0203701, doi:10.1371/JOURNAL.PONE.0203701.

Zhao, Y.; Wang, M.Y.; Hao, K.; Chen, X.Q.; Du, J.Z. CRHR1 Mediates P53 Transcription Induced by High Altitude Hypoxia through ERK 1/2 Signaling in Rat Hepatic Cells. *Peptides (N.Y.)*2013, *44*, 8–14, doi:10.1016/J.PEPTIDES.2013.03.023.

Zinkernagel, A.S.; Johnson, R.S.; Nizet, V. Hypoxia Inducible Factor (HIF) Function in Innate Immunity and Infection. *J Mol Med*2007, *85*, 1339–1346, doi:10.1007/S00109-007-0282-2/FIGURES/1.