

Unraveling the Biomarker Prospects of High-Altitude Diseases: Insights from Biomolecular Event Network Constructed using Text Mining

Supplementary Data-1

Identified bio-molecular events with PMID and corresponding abstracts

15132953 "Greater vascularity, lowered HIF-1/DNA binding, and elevated GSH as markers of adaptation to in vivo chronic hypoxia. Vascularity is increased in placentas from high- compared with low-altitude pregnancies. An angiogenic response to hypoxia may protect an organ from further hypoxic insult by increasing blood flow and oxygen delivery to the tissue. We hypothesized that increased placental vascularity is sufficient to adapt to high altitude. Therefore, indexes of hypoxic stress would not be present in placentas from successful high-altitude pregnancies. Full-thickness placental biopsies were 1) collected and frozen in liquid nitrogen within 5 min of placental delivery and 2) fixed in formalin for stereologic analyses at high (3,100 m, n = 10) and low (1,600 m, n = 10) altitude. Hypoxia-inducible transcription factor (HIF-1) activity was analyzed by ELISA. Western blot analyses were used to evaluate HIF-1alpha, HIF-1beta, HIF-2alpha, von Hippel-Lindau protein, VEGF, Flt-1, enolase, and GAPDH. Magnetic resonance spectroscopy was used to evaluate endogenous metabolism. The ratio of placental capillary surface density to villous surface density was 70% greater at high compared with low altitude. HIF-1 activity and HIF-1-associated proteins were unchanged in placentas from high- vs. low-altitude pregnancies. Placental expression of HIF-1-mediated proteins VEGF, Flt-1, enolase, and GAPDH were unchanged at high vs. low altitude. Succinate, GSH, phosphomonoesters, and ADP were elevated in placenta from high compared with low altitude. Placentas from uncomplicated high-altitude pregnancies have greater vascularity and no indication of significant hypoxic stress at term compared with placentas from low altitude."

T0	Protein 883 888	HIF-1
T1	Protein 972 982	HIF-1alpha
T2	Protein 984 1032	HIF-1beta , HIF-2alpha , von Hippel-Lindau protein
T3	Protein 1034 1038	VEGF
T4	Protein 1279 1284	HIF-1
T5	Protein 1425 1453	HIF-1-mediated proteins VEGF
T1043	Gene_expression 1410 1420	
E125	Gene_expression:T1043	Theme:T5

15649874 "Greater free plasma VEGF and lower soluble VEGF receptor-1 in acute mountain sickness. Vascular endothelial growth factor (VEGF) is a hypoxia-induced protein that produces vascular permeability, and limited evidence suggests a possible role for VEGF in the pathophysiology of acute mountain sickness (AMS) and/or high-altitude cerebral edema (HACE). Previous studies demonstrated

that plasma VEGF alone does not correlate with AMS; however, soluble VEGF receptor (sFlt-1), not accounted for in previous studies, can bind VEGF in the circulation, reducing VEGF activity. In the present study, we hypothesized that free VEGF is greater and sFlt-1 less in subjects with AMS compared with well individuals at high altitude. Subjects were exposed to 4,300 m for 19-20 h (baseline 1,600 m). The incidence of AMS was determined by using a modified Lake Louise symptom score and the Environmental Symptoms Questionnaire for cerebral effects. Plasma was collected at low altitude and after 24 h at high altitude, or at time of illness, and then analyzed by ELISA for VEGF and for soluble VEGF receptor, sFlt-1. AMS subjects had lower sFlt-1 at both low and high altitude compared with well subjects and a significant rise in free plasma VEGF on ascent to altitude compared with well subjects. We conclude that increased free plasma VEGF on ascent to altitude is associated with AMS and may play a role in pathophysiology of AMS."

T0 Protein 55 70 VEGF receptor-1
T1 Protein 99 139 Vascular endothelial growth factor (VEGF
T2 Protein 273 277 VEGF
T3 Protein 487 501 VEGF receptor
T4 Protein 571 575 VEGF
T5 Protein 607 611 VEGF
T6 Protein 1167 1180 VEGF receptor
T7 Protein 1326 1330 VEGF
T1044 Binding 565 569
E126 Binding:T1044 Theme:T3
E127 Binding:T1044 Theme:T4
E128 Binding:T1044 Theme:T5
E129 Binding:T1044 Theme:T3 Theme2:T4
E130 Binding:T1044 Theme:T3 Theme2:T5
E131 Binding:T1044 Theme:T4 Theme2:T3
E132 Binding:T1044 Theme:T4 Theme2:T5
E133 Binding:T1044 Theme:T5 Theme2:T3
E134 Binding:T1044 Theme:T5 Theme2:T4

22595196 "EPAS1 and EGLN1 associations with high altitude sickness in Han and Tibetan Chinese at the Qinghai-Tibetan Plateau. High altitude sickness (HAS) occurs among humans visiting or inhabiting high altitude environments. Genetic differences in the EPAS1 and EGLN1 genes have been found between lowland (Han) and highland (Tibetan) Chinese. Three SNPs within EPAS1 and EGLN1 were evaluated in Han and Tibetan patients with acute mountain sickness (AMS) and chronic mountain sickness (CMS). We compared 85 patients with AMS to 79 Han unaffected with mountain sickness (MS) as well as 45 CMS patients to 34 unaffected Tibetan subjects. The three SNPs studied were EPAS1

[ch2: 46441523 (hg18), EGLN1 (rs480902) and (rs516651). Direct sequencing was used to identify individual genotypes for the three SNPs. Age was found to be significantly associated with the EPAS1 SNP in the CMS patients while heart rate (HR) and oxygen saturation level of hemoglobin (SaO₂) were found to be significantly associated with the EGLN1 (rs480902) SNP in the Han patients with AMS. The individuals with CMS were found to diverge significantly for the EPAS1 SNP compared to their Tibetan control group as measured by genetic distance (0.123) indicating positive selection of the EPAS-G allele with age and illness. The EGLN1 (rs480902) SNP had a significant correlation with hematocrit (HCT), HR and SaO₂ in AMS patients. AMS and CMS were found to be significantly associated with the EPAS1 and EGLN1 SNPs compared to their Han and Tibetan control groups, respectively, indicating these nucleotide alterations have a physiological effect for the development of high altitude sickness."

T0	Protein 278 290 EGLN1 genes
T1	Protein 732 737 EGLN1
T2	Protein 913 923 EPAS1 SNP
T3	Protein 999 1009 hemoglobin
T4	Protein 1079 1084 EGLN1
T5	Protein 1343 1356 EPAS-G allele
T6	Protein 1386 1391 EGLN1
T7	Protein 1570 1575 EPAS1
T8	Protein 1582 1593 EGLN1 SNPs
T1003	Binding 889 899
T1004	Binding 1055 1065
A16	Source E4 Current
A17	Manner E4 High
A18	CL E4 L3
A19	KT E4 Observation
A20	Polarity E4 Positive
E4	Binding:T1003 Theme:T2
A21	Source E5 Current
A22	Manner E5 High
A23	CL E5 L3
A24	KT E5 Observation
A25	Polarity E5 Positive
E5	Binding:T1004 Theme:T3

20977927 "Regulation of bone marrow hematopoietic stem cell is involved in high-altitude erythrocytosis. OBJECTIVE: Hypoxia at high altitudes can lead to increased production of red blood cells through the hormone erythropoietin (EPO). In this study, we observed how the EPO-unresponsive hematopoietic stem cell (HSC) compartment responds to high-altitude hypoxic environments and contributes to erythropoiesis. MATERIALS AND METHODS: Using a mouse model at simulated high altitude, the bone marrow (BM) and spleen lineage marker(-)Sca-1(+)c-Kit(+) (LSK) HSC compartment were observed in detail. Normal LSK cells were then cultured under different conditions (varying EPO levels, oxygen concentrations, and BM supernatants) to investigate the causes of the HSC responses. RESULTS: Hypoxic mice exhibited a marked expansion in BM and spleen LSK compartments, which were associated with enhanced proliferation. BM HSCs seemed to play a more important role in erythropoiesis at high altitude than spleen HSCs. There was also a lineage fate change of BM HSCs in hypoxic mice that was manifested in increased megakaryocyte-erythrocyte progenitors and periodically reduced granulocyte-macrophage progenitors in the BM. The LSK cells in hypoxic mice displayed upregulated erythroid-specific GATA-1 and downregulated granulocyte-macrophage-specific PU.1 messenger RNA expression, as well as the capacity to differentiate into more erythroid precursors after culture. BM culture supernatant from hypoxic mice (but not elevated EPO or varying O₂ tension) could induce expansion and erythroid-priority differentiation of the HSC population, a phenomenon partially caused by increasing interleukin-3 and interleukin-6 secretion in the BM. CONCLUSIONS: The present study suggests a new EPO-independent HSC mechanism of high-altitude erythrocytosis."

T0 Protein 560 576 Sca-1 (+) c-Kit (+)

T1 Protein 1407 1425 PU.1 messenger RNA

T2 Protein 1786 1799 interleukin-6

T1005 Gene_expression 1426 1436

T1006 Localization 1801 1810

A26 Source E6 Current

A27 KT E6 Gen-Other

A28 CL E6 L3

A29 Manner E6 Neutral

A30 Polarity E6 Positive

E6 Gene_expression:T1005 Theme:T1

A31 Source E7 Current

A32 CL E7 L3

A33 Manner E7 Neutral

A34 KT E7 Observation

A35 Polarity E7 Positive

E7 Localization:T1006 Theme:T2

14754397 "Erythropoietin withdrawal leads to the destruction of young red cells at the endothelial-macrophage interface. Erythropoietin is a growth factor for endothelial cells as well as for erythroid cells. In contrast to their proliferative response to physiological levels of erythropoietin, endothelial cells may respond to decreased levels by triggering a process called neocytolysis. Neocytolysis is the selective destruction of the youngest circulating red cells, which may be prompted by endothelial cells communicating with macrophages to stimulate phagocytosis of this unusual cell subset. We speculate that this is due to decreased production by endothelial cells of the macrophage-deactivating transforming growth factor-beta. The resulting proinflammatory phenotype may include macrophage production of thrombospondin, which forms bridges between adhesion molecules selectively expressed on young red cells (CD36) and the CD36/alphavbeta3 complex on macrophages that triggers phagocytosis. Alternatively, inflammatory mediators secreted by endothelial cells and macrophages during erythropoietin withdrawal may signal young red cells to expose phosphatidylserine, which would mark them for elimination via the normal pathway for aged red cell destruction. Neocytolysis has been demonstrated in returning astronauts and in polycythemic individuals at high altitude on descent to sea level. It contributes to the anemia of renal disease, is triggered by the rapidly falling levels of erythropoietin seen after intravenous administration, and may be the normal mechanism for reduction of red cell mass in newborns. It may play a role in chronic diseases including malaria and sickle cell anemia. New erythropoietin products and methods of administration avoid the intermittent rapid decreases associated with the stimulus for neocytolysis, but study of this phenomenon may yield further improvements in drug design."

T0 Protein 10 24 Erythropoietin
T1 Protein 124 138 Erythropoietin
T2 Protein 294 308 erythropoietin
T3 Protein 990 1015 CD36/alphavbeta3 complex
T4 Protein 1160 1174 erythropoietin
T5 Protein 1587 1601 erythropoietin
T1007 Gene_expression 945 954
T1008 Planned_process 1628 1642
A36 Source E8 Current
A37 KT E8 Gen-Other
A38 CL E8 L3
A39 Manner E8 Neutral
A40 Polarity E8 Positive
E8 Gene_expression:T1007 Theme:T3
A41 Source E9 Current
A42 CL E9 L3
A43 Manner E9 Neutral
A44 KT E9 Observation
A45 Polarity E9 Positive

E9 Planned_process:T1008 Instrument:T5

14713116 "Hypoxia and high altitude. The molecular response. Increased erythropoietin plasma levels and the consequent augmented production of red blood cells is the best known systemic adaptation to reduced oxygen partial pressure (pO₂). Intensive research during the last years revealed that the molecular mechanism behind the regulation of erythropoietin is ubiquitous and has far more implications than first thought. Erythropoietin regulation results from the activation of the hypoxia-inducible factor-1 (HIF-1) pathway under hypoxic conditions. HIF-1 is a heterodimer consisting of an oxygen sensitive--HIF-1--and an oxygen-independent subunit--HIF-1beta (also known as the aryl hydrocarbon receptor nuclear translocator--ARNT). In addition to erythropoietin, more than 30 genes are now known to be up-regulated by HIF-1. Recently, the critical involvement of HIF-1alpha post-translational modifications in the cellular oxygen sensing mechanism was discovered. In this review we will focus on the regulation of the HIF-1 pathway and the cellular oxygen sensor and discuss their implications in high altitude hypoxia."

T0 Protein 74 88 erythropoietin

T1 Protein 364 378 erythropoietin

T2 Protein 447 461 Erythropoietin

T3 Protein 518 551 hypoxia-inducible factor-1 (HIF-1

T4 Protein 591 596 HIF-1

T5 Protein 694 703 HIF-1beta

T6 Protein 724 779 aryl hydrocarbon receptor nuclear translocator -- ARNT

T7 Protein 799 813 erythropoietin

T8 Protein 927 937 HIF-1alpha

T9 Protein 1089 1094 HIF-1

T1045 Positive_regulation 63 72

T1046 Regulation 348 358

T1047 Regulation 1069 1079

E135 Positive_regulation:T1045 Theme:T0

E136 Regulation:T1046 Theme:T1

E137 Regulation:T1047 Theme:T9

23840253 "Rhodiola crenulata and Its Bioactive Components, Salidroside and Tyrosol, Reverse the Hypoxia-Induced Reduction of Plasma-Membrane-Associated Na,K-ATPase Expression via Inhibition of ROS-AMPK-PKC xi Pathway. Exposure to hypoxia leads to impaired pulmonary sodium transport, which is associated with Na,K-ATPase dysfunction in the alveolar epithelium. The present study is designed to examine the effect and mechanism of Rhodiola crenulata extract (RCE) and its bioactive components on hypoxia-mediated Na,K-ATPase endocytosis. A549 cells were exposed to hypoxia in the presence or

absence of RCE, salidroside, or tyrosol. The generation of intracellular ROS was measured by using the fluorescent probe DCFH-DA, and the endocytosis was determined by measuring the expression level of Na,K-ATPase in the PM fraction. Rats exposed to a hypobaric hypoxia chamber were used to investigate the efficacy and underlying mechanism of RCE in vivo. Our results showed that RCE and its bioactive compounds significantly prevented the hypoxia-mediated endocytosis of Na,K-ATPase via the inhibition of the ROS-AMPK-PKC zeta pathway in A549 cells. Furthermore, RCE also showed a comparable preventive effect on the reduction of Na,K-ATPase endocytosis and inhibition of AMPK-PKC xi pathway in the rodent model. Our study is the first to offer substantial evidence to support the efficacy of Rhodiola products against hypoxia-associated Na,K-ATPase endocytosis and clarify the ethnopharmacological relevance of Rhodiola crenulata as a popular folk medicine for high-altitude illness."

T0 Protein 155 163 K-ATPase
T1 Protein 322 330 K-ATPase
T2 Protein 535 543 K-ATPase
T3 Protein 628 631 RCE
T4 Protein 834 842 K-ATPase
T5 Protein 1119 1127 K-ATPase
T6 Protein 1158 1175 ROS-AMPK-PKC zeta
T7 Protein 1288 1296 K-ATPase
T8 Protein 1512 1520 K-ATPase
T1048 Negative_regulation 112 121
T1049 Gene_expression 164 174
T1050 Gene_expression 808 818
E138 Negative_regulation:T1048 Theme:T0
E139 Negative_regulation:T1048 Theme:E140
E140 Gene_expression:T1049 Theme:T0
E141 Gene_expression:T1049 Theme:T1
E142 Gene_expression:T1050 Theme:T4

10704252 "High altitude increases circulating interleukin-6, interleukin-1 receptor antagonist and C-reactive protein. Hypoxic pulmonary vasoconstriction is associated with but may not be sufficient for the development of high-altitude pulmonary oedema (HAPO). Hypoxia is known to induce an inflammatory response in immune cells and endothelial cells. It has been speculated that hypoxia-induced inflammatory cytokines at high altitude may contribute to the development of HAPO by causing capillary leakage in the lung. We were interested if such an inflammatory response, possibly involved in a later development of HAPO, is detectable at high altitude in individuals without HAPO. We examined the plasma levels of interleukin 6 (IL-6), interleukin 1 receptor antagonist (IL-1ra) and C-reactive protein (CRP) in two independent studies: study A, Jungfrauoch, Switzerland, three overnight stays at 3458 m, n=12; study B: Capanna Regina Margherita, Italy, 3 overnight stays at 3647 m and one overnight

stay at 4559 m, n=10. In both studies, probands showed symptoms of acute mountain sickness but no signs of HAPO. At the Jungfrauoch, IL-6 increased from 0.1+/-0.03 pg/ml to 2.0+/-0.5 pg/ml (day 2, P=0.03), IL-1ra from 101+/-21 to 284+/-73 pg/ml (day 2, P=0.01), and CRP from 1.0+/-0.4 to 5.8+/-1.5 micrograms/ml (day 4, P=0.01). At the Capanna Margherita, IL-6 increased from 0.5+/-0.2 pg/ml to 2.0+/-0.8 pg/ml (P=0.02), IL-1ra from 118+/-25 to 213+/-28 pg/ml (P=0.02), and CRP from 0.4+/-0.03 to 3.5+/-1.1 micrograms/ml (P=0.03). IL-8 was below the detection limit of the ELISA (<25 pg/ml) in both studies. The increase of IL-6 and IL-1ra in response to high altitude was delayed and preceded the increase of CRP. We conclude that: (1) circulating IL-6, IL-1ra and CRP are upregulated in response to hypobaric hypoxic conditions at high altitude, and (2) the moderate systemic increase of these inflammatory markers may reflect considerable local inflammation. The existence and the kinetics of high altitude-induced cytokines found in this study support the hypothesis that inflammation is involved in the development of HAPO."

T0 Protein 63 86 interleukin-1 receptor

T1 Protein 767 780 interleukin 6

T2 Protein 791 814 interleukin 1 receptor

T3 Protein 1635 1639 IL-8

T4 Protein 2283 2289 HAPO . "

T1051 Positive_regulation 25 34

E143 Positive_regulation:T1051 Theme:T0

22595196 "EPAS1 and EGLN1 associations with high altitude sickness in Han and Tibetan Chinese at the Qinghai-Tibetan Plateau. High altitude sickness (HAS) occurs among humans visiting or inhabiting high altitude environments. Genetic differences in the EPAS1 and EGLN1 genes have been found between lowland (Han) and highland (Tibetan) Chinese. Three SNPs within EPAS1 and EGLN1 were evaluated in Han and Tibetan patients with acute mountain sickness (AMS) and chronic mountain sickness (CMS). We compared 85 patients with AMS to 79 Han unaffected with mountain sickness (MS) as well as 45 CMS patients to 34 unaffected Tibetan subjects. The three SNPs studied were EPAS1 [ch2: 46441523 (hg18)], EGLN1 (rs480902) and (rs516651). Direct sequencing was used to identify individual genotypes for the three SNPs. Age was found to be significantly associated with the EPAS1 SNP in the CMS patients while heart rate (HR) and oxygen saturation level of hemoglobin (SaO₂) were found to be significantly associated with the EGLN1 (rs480902) SNP in the Han patients with AMS. The individuals with CMS were found to diverge significantly for the EPAS1 SNP compared to their Tibetan control group as measured by genetic distance (0.123) indicating positive selection of the EPAS-G allele with age and illness. The EGLN1 (rs480902) SNP had a significant correlation with hematocrit (HCT), HR and SaO₂ in AMS patients. AMS and CMS were found to be significantly associated with the EPAS1 and EGLN1 SNPs compared to their Han and Tibetan control groups, respectively, indicating these nucleotide alterations have a physiological effect for the development of high altitude sickness."

T0 Protein 278 290 EGLN1 genes

T1 Protein 732 737 EGLN1

T2 Protein 913 923 EPAS1 SNP

T3	Protein 999 1009	hemoglobin
T4	Protein 1079 1084	EGLN1
T5	Protein 1343 1356	EPAS-G allele
T6	Protein 1386 1391	EGLN1
T7	Protein 1570 1575	EPAS1
T8	Protein 1582 1593	EGLN1 SNPs
T1019	Binding 889 899	
T1020	Binding 1055 1065	
A106	Source E22 Current	
A107	Manner E22 High	
A108	CL E22 L3	
A109	KT E22 Observation	
A110	Polarity E22 Positive	
E22	Binding:T1019 Theme:T2	
A111	Source E23 Current	
A112	Manner E23 High	
A113	CL E23 L3	
A114	KT E23 Observation	
A115	Polarity E23 Positive	
E23	Binding:T1020 Theme:T3	

11803115 "Upregulation of adrenocorticotrophic hormone in the corticotrophs and downregulation of surface receptors and antigens on the macrophages in the adenohypophysis following an exposure to high altitude. Altitude exposures lead to the development of hypobaric hypoxia because of low oxygen tension in the ambient air. This study has shown the vigorous upregulation of adrenocorticotrophic hormone (ACTH) expression in corticotrophs of the pars distalis (adenohypophysis) of rats 1-7 days after an altitude exposure. Concomitant to this was the increase in number and hypertrophy of the immunoreactive corticotrophs. It was suggested that this had resulted in an upsurge of ACTH production which may have suppressed the immuno-expression of complement type 3 receptors and major histocompatibility complex class II antigens constitutively expressed by the parenchymal macrophages through paracrine action. Along with ACTH, altered levels of other hormones following such exposures may also contribute to suppression of antigen presenting function and phagocytic activity of macrophages. The effects of altitude (hypobaric hypoxia) exposure, however, were reversible as the above immunohistochemical changes returned to normal 21-28 days after the hypobaric hypoxic insult."

T0 Protein 421 425 ACTH

T1 Protein 706 710 ACTH

T2 Protein 781 865 complement type 3 receptors and major histocompatibility complex class II antigens

T1052 Gene_expression 428 438

T1053 Positive_regulation 695 702

T1054 Gene_expression 712 722

T1055 Negative_regulation 744 754

T1056 Gene_expression 767 777

T1057 Gene_expression 882 891

E144 Gene_expression:T1052 Theme:T0

E145 Positive_regulation:T1053 Theme:T1

E146 Positive_regulation:T1053 Theme:E147

E147 Gene_expression:T1054 Theme:T1

E148 Gene_expression:T1054 Theme:T2

E149 Negative_regulation:T1055 Theme:E150

E150 Gene_expression:T1056 Theme:T1

E151 Gene_expression:T1056 Theme:T2

E152 Gene_expression:T1057 Theme:T1

E153 Gene_expression:T1057 Theme:T2

11529286 "Response of nitric oxide pathway to L-arginine infusion at the altitude of 4,350 m. It was hypothesized that hypoxia may inhibit nitric oxide (NO) production by reducing the availability of endothelial NO synthase (NOS III) substrate. To evaluate the effect of L-arginine on the NO release in high altitude, 11 subjects were infused with L-arginine (0.5 g x kg⁻¹) during 30 min in normoxia and after 36 h at 4,350 m (hypoxia). The L-citrulline and cyclic guanosine monophosphate (cGMP) concentrations were measured to investigate NO synthesis and guanylyl cyclase activity respectively. L-citrulline concentration, arterial oxygen saturation (Sa,O₂), systemic blood pressure, heart rate and acute mountain sickness (AMS) score were measured at rest and 15, 30 and 45 min after starting infusion. The results showed that baseline L-citrulline was lower in hypoxia (p<0.05). L-arginine infusion increased L-citrulline concentration in both conditions. However, in hypoxia L-citrulline concentration remained lower than in normoxia (p<0.05). The concentration of cGMP was lower in hypoxia (p<0.05). In hypoxia, Sa,O₂ increased from 15 min after the start of the infusion to 45 min (p<0.05). Blood pressure and heart rate were not affected by L-arginine infusion. Subjects who experienced symptoms of AMS showed a slight decrease in AMS score with L-arginine. The decreased L-citrulline suggests a hypoxia-induced impairment of nitric oxide synthase III or a decrease in L-arginine availability. The improvement of arterial oxygen saturation by pretreatment with L-arginine could be ascribed to an enhancement of the ventilation/perfusion ratio. Collectively, these results are consistent with a decrease in nitric oxide production in hypoxia that could be antagonized by supplying nitric oxide synthase cosubstrate."

T0 Protein 213 245 endothelial NO synthase (NOS III
T1 Protein 1517 1542 nitric oxide synthase III
T1058 Negative_regulation 1549 1557
E154 Negative_regulation:T1058 Theme:T1

12614929 "Gene expression in the Andes; relevance to neurology at sea level. Chronic mountain sickness (CMS), a maladaptation syndrome to chronic hypoxia, occurs in the Andes. Gene expression differences in Andeans could explain adaptation and maladaptation to hypoxia, both of which are relevant to neurology at sea level. Expression of genes responsive to cellular oxygen concentration, hypoxia-inducible factor-1alpha (HIF-1alpha), three splicing variants of vascular endothelial growth factor (VEGF) and von Hippel-Lindau protein (pVHL) was measured by reverse transcription polymerase chain reaction (RT-PCR) in 12 Cerro de Pasco (CP) (altitude 4338 m) natives and 15 CMS patients in CP. Thirteen high altitude natives living in Lima and five Lima natives were sea level controls. A CMS score (CMS-sc) was assigned clinically. Expression was related to the clinical assessment. High expression of HIF-1alpha and VEGF-121 was found in CMS ($P<0.001$). Samples from CP had higher expression than those from Lima ($P<0.001$). Expression of HIF-1alpha and VEGF-121 was related to age ($P<0.001$); adjusting for age did not abolish the group effect. Higher CMS-sc was related to expression independent of age ($P<0.001$). VEGF-165 and -189 were expressed only in CMS. Birth altitude had no effect on gene expression. pVHL was not quantifiable. HIF-1alpha and VEGF-121 participate in adaptation to hypoxia. The high levels may explain blood vessel proliferation in Andeans and hold lessons for patients at sea level. VEGF-165 expression suggests that it contributes to preservation of neuronal function in human chronic hypoxia. VHL mutations may mark those destined to develop neural crest tumors which are common in the Andes."

T0 Protein 475 509 vascular endothelial growth factor
T1 Protein 511 515 VEGF
T2 Protein 522 556 von Hippel-Lindau protein (pVHL
T3 Protein 932 942 HIF-1alpha
T4 Protein 1082 1092 HIF-1alpha
T1059 Gene_expression 335 345
T1060 Positive_regulation 911 915
T1061 Gene_expression 917 927
T1062 Gene_expression 1068 1078
E155 Gene_expression:T1059 Theme:T0
E156 Gene_expression:T1059 Theme:T1
E157 Gene_expression:T1059 Theme:T2
E158 Positive_regulation:T1060 Theme:E159

E159 Gene_expression:T1061 Theme:T3

E160 Gene_expression:T1062 Theme:T4

12743791 "Association of high-altitude systemic hypertension with the deletion allele-of the angiotensin-converting enzyme (ACE) gene. People who visit high-altitude areas are exposed to a stressful environment and a good percentage of them suffer from high-altitude-induced diseases, including systemic hypertension. Identification of genetic markers for high-altitude-induced diseases would help to reduce the rate of morbidity/mortality from such diseases. The development of systemic hypertension on exposure to high altitude (3,500 m) for 30 days in otherwise normotensive natives of low-altitudes was investigated. The angiotensin-converting enzyme (ACE) insertion/deletion (I/D) genotypes and renin-angiotensin-aldosterone system were simultaneously studied. In the hypertensives during their stay at high altitude, the ACE D allele frequency was significantly higher than in the normotensives (0.67 versus 0.32 $\chi^2(1) = 10.6$, $P < 0.05$). In the normotensives during their stay at high altitude, there was no significant increase in plasma aldosterone levels despite increased plasma renin activity. Results of the present study suggest that environmental changes and pre-existing genetic factors, namely the ACE D allele, might be two of the factors predisposing natives of low altitudes to systemic hypertension, a polygenic disease, at high altitude."

T0 Protein 130 133 ACE

T1 Protein 860 883 ACE D allele frequency

T2 Protein 1142 1147 renin

T3 Protein 1279 1292 ACE D allele

T1063 Positive_regulation 1123 1132

E161 Positive_regulation:T1063 Theme:T2

12918255 "[Expression of markers of immunocompetent cells, cytokine level, and L-arginine metabolism in complex extremely high frequency and interferon therapy of inflammatory diseases in women of highlands]. Chronic inflammatory gynecological diseases (CIGD) in highlanders (2,100-2,200 m a.s.l.) are accompanied with the following changes in immunoregulatory parameters: strengthening in the expression of CD3+ (TCR), CD4+ (T-helpers), CD16+ (NK-cells), CD25+ (activated IL-2R), increase in CD4+/CD8+ ratio, levels of circulating cytokines--alpha-, beta-, gamma-interferon (IFN) and alpha-, beta-tumor necrotizing factor (TNF), strengthening in immune adhesion of thrombocytes (IAT), and inhibition of the oxidative metabolic way of L-arginine with redistribution of the main metabolites formed via its non-oxidative way. Complex extremely high frequency (EHF) therapy and interferon (with Laferon) therapy of CIGD normalized expression of the differentiated and functional CD-markers of immunocompetent cells (ICC), CD4+/CD8+ ratio, increased expression of CD8+, decreased IAT and levels of circulating cytokines (IFN, TNF), changed L-arginine metabolism with activation of the oxidative way. Full-value of the population signs of immune stabilization due to the treatment was complemented with increase in the ICC functional parameters--markers of mitochondrial, lysosomal and mitotic activity. We first demonstrated a high effectiveness of complex use of EHF and Laferon as an immunocorrective therapy of CIGD in highlanders."

T0 Protein 424 428 CD3+

T1 Protein 472 494 CD25+ (activated IL-2R
T2 Protein 613 647 beta-tumor necrotizing factor (TNF
T1064 Gene_expression 409 419
E162 Gene_expression:T1064 Theme:T0
E163 Gene_expression:T1064 Theme:T1
E164 Gene_expression:T1064 Theme:T2

20920561 "Salidroside promotes erythropoiesis and protects erythroblasts against oxidative stress by up-regulating glutathione peroxidase and thioredoxin. ETHNOPHARMACOLOGICAL RELEVANCE: Rhodiola rosea is commonly used in China and Tibet folk medicine for the treatment of high altitude sickness, anoxia and mountain malhypoxia. AIM OF STUDY: Salidroside (SDS) is an active ingredient of Rhodiola rosea. This study attempted to examine the potential erythropoiesis-stimulating and anti-oxidative effect of SDS in TF-1 erythroblasts. MATERIALS AND METHODS: The erythropoiesis-promoting effect was determined by treating human TF-1 cells, one of the popular in vitro models for studying erythropoiesis, with SDS in the presence and absence of erythropoietin (EPO) through the measurement of the expression of a series of erythroid markers such as glycophorin A (GPA), transferrin receptor (CD71) and hemoglobin (Hb). The potential protective effect of SDS against H(2)O(2)-induced apoptosis and its underlying mechanism in TF-1 erythroblasts were examined by flow cytometry and Western blot analysis. RESULTS: SDS promotes erythropoiesis in the EPO-treated cells and it also reduces the number of apoptotic cells in TF-1 erythroblasts after H(2)O(2) treatment probably through the up-regulation of protective proteins thioredoxin-1 (Trx1) and glutathione peroxidase-1 (GPx1). CONCLUSION: Our study provides evidence to explain the ethnopharmacological role of SDS and Rhodiola rosea in Chinese medicine. Our findings also support the use of SDS as an erythropoiesis-adjuvant agent to correct anemia and malhypoxia."

T0 Protein 131 141 peroxidase
T1 Protein 777 791 erythropoietin
T2 Protein 888 901 glycophorin A
T3 Protein 911 933 transferrin receptor
T4 Protein 937 941 CD71
T5 Protein 947 957 hemoglobin
T6 Protein 1426 1438 peroxidase-1
T7 Protein 1440 1444 GPx1
T1065 Negative_regulation 764 771
T1066 Gene_expression 833 843
T1067 Positive_regulation 1349 1362
E165 Negative_regulation:T1065 Theme:T1
E166 Gene_expression:T1066 Theme:T1

E167 Gene_expression:T1066 Theme:T2
 E168 Gene_expression:T1066 Theme:T3
 E169 Gene_expression:T1066 Theme:T4
 E170 Gene_expression:T1066 Theme:T5
 E171 Positive_regulation:T1067 Cause:T7 Theme:T6
 E172 Positive_regulation:T1067 Theme:T7

21393362 "Polymorphisms of renin--angiotensin system genes as a risk factor for high-altitude pulmonary oedema. The genes of the renin--angiotensin system (RAS) play an important role in the regulation of pulmonary vascular tone. Although studies on individual genes polymorphisms have reported association with high-altitude pulmonary oedema (HAPE), studies on multiple genes or epistasis are lacking. We therefore investigated the association of the RAS polymorphisms with HAPE. In a case-control design, we screened 163 HAPE-resistant/controls (HAPE-r) and 160 HAPEpatients (HAPE-p) of Indian origin for eight polymorphisms of four RAS genes, ACE, AGT, AGTR1 and AGTR2. Significant difference in genotype and allele frequencies of the ACE I/D and AGT M235T polymorphisms was observed between HAPE-p and HAPE-r ($p < 0.05$). In three-locus haplotype analysis of AGT the haplotype GTM was significantly higher in HAPE-p (29%) and haplotype GTT in HAPE-r (27%) after Bonferroni correction ($p < 0.006$). The differences were insignificant for polymorphisms from AGTR1 and AGTR2. The MDR (multifactor dimensional reduction) approach for gene--gene interaction depicted individual polymorphism M235T as the best disease predicting model (cross validation consistency, CVC = 10/10). We found a significant association of D allele of ACE and M allele of AGT with HAPE. The findings are supported at the haplotypic level as well as through nested genetic interaction between the RAS gene polymorphisms using the MDR approach."

T0 Protein 34 58 angiotensin system genes
 T1 Protein 769 777 ACE I/D
 T2 Protein 1581 1595 MDR approach . "
 T1068 Binding 1520 1531
 E173 Binding:T1068 Theme:T2

15558999 "Renin angiotensin aldosterone system and ACE I/D gene polymorphism in high-altitude pulmonary edema. INTRODUCTION: People who visit high altitude are exposed to a stressful environment, and many of them suffer from altitude-induced conditions, including high altitude pulmonary edema (HAPE). We investigated the renin angiotensin aldosterone system (RAAS) and the possible association of angiotensin converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism in the development of HAPE in Indian men. METHODS: Subjects were all low-altitude natives: 19 men who developed HAPE within 1-3 d of arrival at 3000 to 3800 m (patients); and 20 age-matched men who did not develop HAPE during a period of a month or more at $>$ or $=$ 3500 m (controls). We recorded the arterial oxygen saturation (Sao₂), heart rate (HR), and blood pressure (BP) of both groups and measured their levels of plasma renin activity (PRA), ACE, aldosterone, and serum electrolytes. Polymerase chain

reaction was used to investigate a 287 base pair alu repeat sequence I/D polymorphism in the ACE gene. RESULTS: Compared with controls, patients showed a significantly lower Sao2 and a higher HR. They also had significantly higher plasma PRA, aldosterone, ACE, and serum sodium (Na+) and potassium (K+). No significant difference was observed in ACE I/D allele frequencies. DISCUSSION: The results suggested that RAAS is involved in the development of HAPE in low-altitude natives, but there is no association of ACE I/D gene polymorphism with HAPE."

T0	Protein 52 65	ACE I/D gene
T1	Protein 338 375	renin angiotensin aldosterone system
T2	Protein 419 449	angiotensin converting enzyme
T3	Protein 934 947	plasma renin
T4	Protein 1079 1115	alu repeat sequence I/D polymorphism
T5	Protein 1124 1133	ACE gene
T6	Protein 1464 1468	RAAS
T7	Protein 1569 1582	ACE I/D gene
T8	Protein 1603 1609	HAPE . "
T1069	Binding 403 414	
T1070	Binding 1552 1563	
E174	Binding:T1069	Theme:T1 Theme2:T2
E175	Binding:T1069	Theme:T2 Theme2:T1
M1	Negation E176	
E176	Binding:T1070	Theme:T6 Theme2:T7
M2	Negation E177	
E177	Binding:T1070	Theme:T6 Theme2:T8
M3	Negation E178	
E178	Binding:T1070	Theme:T7 Theme2:T6
M4	Negation E179	
E179	Binding:T1070	Theme:T7 Theme2:T8
M5	Negation E180	
E180	Binding:T1070	Theme:T8 Theme2:T6
M6	Negation E181	
E181	Binding:T1070	Theme:T8 Theme2:T7

15649874 "Greater free plasma VEGF and lower soluble VEGF receptor-1 in acute mountain sickness. Vascular endothelial growth factor (VEGF) is a hypoxia-induced protein that produces vascular permeability, and limited evidence suggests a possible role for VEGF in the pathophysiology of acute mountain sickness (AMS) and/or high-altitude cerebral edema (HACE). Previous studies demonstrated that plasma VEGF alone does not correlate with AMS; however, soluble VEGF receptor (sFlt-1), not accounted for in previous studies, can bind VEGF in the circulation, reducing VEGF activity. In the present study, we hypothesized that free VEGF is greater and sFlt-1 less in subjects with AMS compared with well individuals at high altitude. Subjects were exposed to 4,300 m for 19-20 h (baseline 1,600 m). The incidence of AMS was determined by using a modified Lake Louise symptom score and the Environmental Symptoms Questionnaire for cerebral effects. Plasma was collected at low altitude and after 24 h at high altitude, or at time of illness, and then analyzed by ELISA for VEGF and for soluble VEGF receptor, sFlt-1. AMS subjects had lower sFlt-1 at both low and high altitude compared with well subjects and a significant rise in free plasma VEGF on ascent to altitude compared with well subjects. We conclude that increased free plasma VEGF on ascent to altitude is associated with AMS and may play a role in pathophysiology of AMS."

T0 Protein 55 70 VEGF receptor-1
T1 Protein 99 139 Vascular endothelial growth factor (VEGF
T2 Protein 273 277 VEGF
T3 Protein 487 501 VEGF receptor
T4 Protein 571 575 VEGF
T5 Protein 607 611 VEGF
T6 Protein 1167 1180 VEGF receptor
T7 Protein 1326 1330 VEGF
T1071 Binding 565 569
E182 Binding:T1071 Theme:T3
E183 Binding:T1071 Theme:T4
E184 Binding:T1071 Theme:T5
E185 Binding:T1071 Theme:T3 Theme2:T4
E186 Binding:T1071 Theme:T3 Theme2:T5
E187 Binding:T1071 Theme:T4 Theme2:T3
E188 Binding:T1071 Theme:T4 Theme2:T5
E189 Binding:T1071 Theme:T5 Theme2:T3
E190 Binding:T1071 Theme:T5 Theme2:T4

15725412 "Expression of endothelin-1 in the brain and lung of rats exposed to permanent hypobaric hypoxia. High-altitude hypoxia causes pulmonary hypertension in humans and animals. Endothelin-1 (ET-1) is a novel and long-lasting vasoconstrictor. However, no study has dealt with the effects of a hypobaric

hypoxic environment (HHE) on ET-1 activity in the brain. We examined 134 male rats permanently exposed to the equivalent of 5500 m altitude for 1 to 8 weeks. In these HHE rats, the mean pulmonary arterial pressure was significantly raised. The level of ET-1 protein, measured by enzyme immunoassay, increased rapidly in the lungs on exposure to HHE, but decreased in the brain. The level of ET-1 mRNA, measured by semiquantitative RT-PCR, was raised at 1, 4, and 6 weeks' exposure in the lungs and at 4 or more weeks' exposure in 3 of 8 brain regions. By in situ hybridization and immunohistochemistry of brain sections, ET-1 mRNA and protein were detected in the endothelial cells, neurons, and astrocyte-like cells in control rats. In HHE rats, the immunoreactive intensity for ET-1 protein decreased rapidly with time in these cells within the brain, although a few weakly ET-1 protein-positive cells were detected until 8 weeks' exposure to HHE. Only a few weakly ET-1 mRNA-positive endothelial cells were detected in any HHE rats. Although the reactivity for ET-1 mRNA had decreased significantly in neurons and astrocyte-like cells at 1 and 2 weeks' exposure to HHE, it was again strong in both types of cells at 4 weeks' exposure to HHE. These results raise the possibility that during exposure to HHE, ET-1 production in the lung may play a role in the development of pulmonary hypertension, while a decrease in ET-1 production within the brain may help to protect neurons by preventing or limiting the constriction of cerebral microvessels during the hypoxia induced by HHE."

T0 Protein 188 200 Endothelin-1
T1 Protein 202 206 ET-1
T2 Protein 348 352 ET-1
T3 Protein 582 594 ET-1 protein
T4 Protein 728 737 ET-1 mRNA
T5 Protein 962 971 ET-1 mRNA
T6 Protein 1129 1142 ET-1 protein
T7 Protein 1435 1444 ET-1 mRNA
T8 Protein 1695 1699 ET-1
T9 Protein 1988 1993 HHE . "
T1072 Gene_expression 992 1000
T1073 Negative_regulation 1145 1154
T1074 Negative_regulation 1450 1459
T1075 Gene_expression 1701 1711
E191 Gene_expression:T1072 Theme:T5
E192 Negative_regulation:T1073 Theme:T6
E193 Negative_regulation:T1074 Theme:T7
E194 Gene_expression:T1075 Theme:T8
E195 Gene_expression:T1075 Theme:T9

16333988 "Association of hsp70-2 and hsp-hom gene polymorphisms with risk of acute high-altitude illness in a Chinese population. High-altitude illness (HAI) is a potentially fatal condition involving genetic and environmental components. Accumulated experimental evidence suggests that heat shock proteins (Hsps), especially HSP70, can protect cells and organs against different types of damage. We investigated whether genetic variation in constitutive and inducible hsp70 genes could be associated with risk of HAI. The association between polymorphisms of the HSP70 family genes and risk of HAI was determined in 56 patients with HAI and in 100 matched controls by genotyping for the polymorphisms +190 G/C, +1267 A/G, 2437 G/C in the hsp70-1, hsp70-2, and hsp70-hom genes by using polymerase chain reaction-restriction fragment length polymorphism. The data showed that there was no statistically significant difference in the genotype and allele distributions of hsp70-1, in hsp70-2 allele and hsp70-2 A/A and A/B genotypes, and in allele distribution of hsp70-hom among patients with HAI and controls (chi2 test, $P > 0.05$). However, there was a significantly higher frequency of hsp70-2 B/B and hsp70-hom A/A and B/B genotypes and a significantly lower frequency of the hsp70-hom A/B genotype in the HAI patients compared with the controls ($P < 0.05$ for all). The risk associated with the hsp70-2 B/B and hsp70-hom A/A, A/B, and B/B genotypes were 4.017 (95% CI = 1.496-10.781; $P = 0.004$), 2.434 (95% CI = 1.184-5.003; $P = 0.012$), 0.299 (95% CI = 0.148-0.602, $P = 0.001$), and 5.880 (95% CI = 1.145-30.196, $P = 0.026$), respectively. Our results suggest that individuals with hsp70-2 B/B and hsp70-hom A/B and B/B genotypes may be more susceptible to HAI, whereas those with hsp70-hom A/B genotype may be tolerant to HAI. Further studies in individuals of different age and sex are warranted to elucidate the underlying mechanisms of this association and the possible functions of different genotypes of hsp70-2 and hsp70-hom under hypoxic stress."

T0 Protein 489 500 hsp70 genes
T1 Protein 596 614 HSP70 family genes
T2 Protein 1335 1357 hsp70-hom A/B genotype
T3 Protein 1466 1477 hsp70-2 B/B
T4 Protein 1867 1889 hsp70-hom A/B genotype
T1084 Binding 1443 1453
E208 Binding:T1084 Theme:T3

18410568 "The human side of hypoxia-inducible factor. When humans are exposed to hypoxia, systemic and intracellular changes operate together to minimise hypoxic injury and restore adequate oxygenation. Emerging evidence indicates that the hypoxia-inducible factor (HIF) family of transcription factors plays a central regulatory role in these homeostatic changes at both the systemic and cellular levels. HIF was discovered through its action as the transcriptional activator of erythropoietin, and has subsequently been found to control intracellular hypoxic responses throughout the body. HIF is primarily regulated by specific prolyl hydroxylase-domain enzymes (PHDs) that initiate its degradation via the von Hippel-Lindau tumour suppressor protein (VHL). The oxygen and iron dependency of PHD activity accounts for regulation of the pathway by both cellular oxygen and iron status. Recent studies conducted in patients with rare genetic diseases have begun to uncover the wider importance of the PHD-VHL-HIF axis in systems-level human biology. These studies indicate that, in addition to regulating erythropoiesis, the system plays an important role in cardiopulmonary regulation. This article reviews our current understanding of the importance of HIF in human systems-level physiology, and is modelled around the classic physiological response to high-altitude hypoxia."

T0 Protein 510 524 erythropoietin
T1 Protein 661 704 specific prolyl hydroxylase-domain enzymes
T2 Protein 706 710 PHDs

T3 Protein 759 803 von Hippel-Lindau tumour suppressor protein

T1085 Protein_catabolism 735 746

E209 Protein_catabolism:T1085 Theme:T1

E210 Protein_catabolism:T1085 Theme:T2

E211 Protein_catabolism:T1085 Theme:T3

18331218 "Acute normobaric hypoxia stimulates erythropoietin release. Investigations studying the secretion of EPO (erythropoietin) in response to acute hypoxia have produced mixed results. Further, the errors associated with the various methods used to determine EPO are not well documented. The purpose of the current study was to determine the EPO response of 17 trained male subjects to either an acute bout of normobaric hypoxia (Hy; n = 10) or normoxia (Con; n = 7). A secondary aim was to determine the error associated with the measurement of EPO. After baseline tests, the treatment group (Hy) underwent a single bout of hypoxic exposure (F(I(O(2)))) approximately 0.148; 3100 m) consisting of a 90-min rest period followed by a 30-min exercise phase (50% V(O)(2max)). Venous blood samples were drawn pre (0 min) and post (120 min) each test to assess changes in plasma EPO (DeltaEPO). The control (Con) group was subjected to the same general experimental design, but placed in a normoxic environment (F(I(O(2)))) approximately 0.2093). The Hy group demonstrated a mean increase in EPO [19.3 (4.4) vs. 24.1 (5.1) mU/mL], $p < 0.04$, post 120 min of normobaric hypoxia. The calculated technical error of measurement for EPO was 2.1 mU/mL (9.8%). It was concluded that an acute bout of hypoxia, has the capacity to elevate plasma EPO. This study also demonstrates that the increase in EPO accumulation was 2 times greater than the calculated measurement of error."

T0 Protein 49 63 erythropoietin

T1086 Positive_regulation 36 46

T1087 Localization 65 72

E212 Positive_regulation:T1086 Theme:E213

E213 Localization:T1087 Theme:T0

21599636 "Hypobaric hypoxia preconditioning attenuates acute lung injury during high-altitude exposure in rats via up-regulating heat-shock protein 70. HHP (hypobaric hypoxia preconditioning) induces the overexpression of HSP70 (heat-shock protein 70), as well as tolerance to cerebral ischaemia. In the present study, we hypothesized that HHP would protect against HAE (high-altitude exposure)-induced acute lung injury and oedema via promoting the expression of HSP70 in lungs prior to the onset of HAE. At 2 weeks after the start of HHP, animals were exposed to a simulated HAE of 6000 m in a hypobaric chamber for 24 h. Immediately after being returned to ambient pressure, the non-HHP animals had higher scores of alveolar oedema, neutrophil infiltration and haemorrhage, acute pleurisy (e.g. increased exudate volume, increased numbers of polymorphonuclear cells and increased lung myeloperoxidase activity), increased pro-inflammatory cytokines [e.g. TNF-alpha (tumour necrosis factor-alpha), IL (interleukin)-1beta and IL-6], and increased cellular ischaemia (i.e. glutamate and lactate/pyruvate ratio) and oxidative damage [glycerol, NOx (combined nitrate+nitrite) and 2,3-dihydroxybenzoic acid] markers in the BALF (bronchoalveolar fluid). HHP, in addition to inducing overexpression of HSP70 in the lungs, significantly attenuated HAE-induced pulmonary oedema, inflammation, and ischaemic and oxidative damage in the lungs. The beneficial effects of HHP in preventing the occurrence of HAE-induced pulmonary oedema, inflammation, and ischaemic and oxidative

damage was reduced significantly by pretreatment with a neutralizing anti-HSP70 antibody. In conclusion, HHP may attenuate the occurrence of pulmonary oedema, inflammation, and ischaemic and oxidative damage caused by HAE in part via up-regulating HSP70 in the lungs."

T0 Protein 234 264 HSP70 (heat-shock protein 70
T1 Protein 933 954 lung myeloperoxidase
T2 Protein 1007 1051 e.g. TNF-alpha (tumour necrosis factor-alpha
T3 Protein 1359 1364 HSP70
T1088 Gene_expression 215 229
T1089 Gene_expression 1340 1354
E214 Gene_expression:T1088 Theme:T0
E215 Gene_expression:T1089 Theme:T3

19525401 "Long-term hypoxia increases endothelial nitric oxide synthase expression in the ovine fetal adrenal. This study was designed to test the hypothesis that fetal adrenal nitric oxide synthase (NOS) is elevated in response to long-term hypoxia (LTH). Pregnant ewes were maintained at high altitude (3820 m) for approximately the last 100 days of gestation. Between days 138 and 141 of gestation, adrenal glands were collected from LTH fetuses and age-matched normoxic controls. Quantitative real-time polymerase chain reaction (qRT-PCR) and Western analysis were used to quantify NOS expression, and NOS distribution was examined by immunohistochemistry and double-staining immunofluorescence for endothelial NOS (eNOS) and 17alpha-hydroxylase (CYP17). Neuronal NOS (nNOS) was expressed at very low levels and with no differences between groups. Expression of eNOS was significantly greater in the LTH group compared with control. Neuronal NOS was distributed throughout the cortex while the greatest density of eNOS was observed in the zona fasciculata/reticularis area and eNOS co-localized with CYP17. We conclude that LTH enhances eNOS expression in the inner adrenal cortex which may play a role in regulation of cortisol biosynthesis in the LTH fetus."

T0 Protein 175 210 fetal adrenal nitric oxide synthase
T1 Protein 1317 1328 LTH fetus . "
T1090 Positive_regulation 221 229
T1091 Gene_expression 1199 1209
E216 Positive_regulation:T1090 Theme:T0
E217 Gene_expression:T1091 Theme:T1

19481479 "Genetic adaptation to extreme hypoxia: study of high-altitude pulmonary edema in a three-generation Han Chinese family. Organismal response to hypoxia is essential for critical regulation of erythropoiesis, other physiological functions, and survival. There is evidence of individual variation in response to hypoxia as some but not all of the affected individuals develop polycythemia, and or pulmonary and cerebral edema. A significant population difference in response to hypoxia exist as

many highland Tibetan, Ethiopian, and Andean natives developed adaptive mechanisms to extreme hypoxia. A proportion of non-adapted individuals exposed to high altitude develop pulmonary edema (HAPE), pulmonary hypertension, cerebral edema, and extreme polycythemia. The isolation of causative gene(s) responsible for HAPE and other extreme hypoxia complications would provide a rational basis for specific targeted therapy of HAPE, allow its targeted prevention for at-risk populations, and clarify the pathophysiology of other hypoxic maladaptations. The only suggested genetic linkage among unrelated individuals with HAPE has been with endothelial nitric oxide synthase (eNOS) gene. Here we describe a family with multiple members affected with HAPE in three generations. Families with multiple affected members with HAPE have not been described. We first ruled out linkage of HAPE with the eNOS gene. We then performed an analysis of the whole genome using high-density SNP arrays (Affymetrix v5.0) and, assuming a single gene causation of HAPE, ruled out linkage with 34 other candidate genes. Only the HIF2A haplotype was shared by individuals who exhibit the HAPE phenotype, and work on its possible causative role in HAPE is in progress. The small size of our family does not provide sufficient power for a conclusive analysis of linkage. We hope that collaboration with other investigators with access to more HAPE patients will lead to the identification of gene(s) responsible for HAPE and possibly other maladaptive hypoxic complications."

T0 Protein 1217 1244 nitric oxide synthase (eNOS

T1 Protein 1483 1492 eNOS gene

T1092 Binding 1455 1462

E218 Binding:T1092 Theme:T1

17706837 "Neuroprotective effect of cobalt chloride on hypobaric hypoxia-induced oxidative stress. Hypobaric hypoxia, characteristic of high altitude is known to increase the formation of reactive oxygen and nitrogen species (RONS), and decrease effectiveness of antioxidant enzymes. RONS are involved and may even play a causative role in high altitude related ailments. Brain is highly susceptible to hypoxic stress and is involved in physiological responses that follow. Exposure of rats to hypobaric hypoxia (7619 m) resulted in increased oxidation of lipids and proteins due to increased RONS and decreased reduced to oxidized glutathione (GSH/GSSG) ratio. Further, there was a significant increase in superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione-S-transferase (GST) levels. Increase in heme oxygenase 1 (HO-1) and heat shock protein 70 (HSP70) was also noticed along with metallothionein (MT) II and III. Administration of cobalt appreciably attenuated the RONS generation, oxidation of lipids and proteins and maintained GSH/GSSH ratio similar to that of control cells via induction of HO-1 and MT offering efficient neuroprotection. It can be concluded that cobalt reduces hypoxia oxidative stress by maintaining higher cellular HO-1 and MT levels via hypoxia inducible factor 1alpha (HIF-1alpha) signaling mechanisms. These findings provide a basis for possible use of cobalt for prevention of hypoxia-induced oxidative stress."

T0 Protein 785 807 glutathione peroxidase

T1 Protein 873 890 heme oxygenase 1

T2 Protein 893 897 HO-1

T3 Protein 1194 1198 HO-1

T4 Protein 1376 1421 hypoxia inducible factor 1alpha (HIF-1alpha

T1093 Positive_regulation 743 751
T1094 Positive_regulation 860 868
T1095 Positive_regulation 1180 1189
E219 Positive_regulation:T1093 Theme:T0
M9 Negation E220
E220 Positive_regulation:T1094 Theme:T2
E221 Positive_regulation:T1095 Cause:T4 Theme:T3

20367053 "Cytokine mRNA expressions after racing at a high altitude and at sea level in horses with exercise-induced pulmonary hemorrhage. OBJECTIVE: To determine concentrations of cytokine mRNA in horses with exercise-induced pulmonary hemorrhage (EIPH) after racing. ANIMALS: 97 Thoroughbreds. PROCEDURES: Following tracheobronchoscopy, the severity of EIPH was graded (scale of 0 to 4), and venous blood samples were collected from 10 horses in each grade. After RNA isolation and cDNA synthesis, real-time PCR assay was conducted to detect cytokinespecific mRNA for interleukin (IL)-1, IL-6, and IL-10; interferon (INF)-gamma; and tumor necrosis factor (TNF)-alpha. RESULTS: Neither location nor grade of EIPH affected the expression of IL-1 and INF-gamma. There was significantly greater overall expression of IL-6 mRNA at sea level, with significantly more IL-6 expressed in horses with grade 4 EIPH than in horses with grade 0, 1, or 2 EIPH. At a high altitude, no difference was detected for IL-6 expression among the various EIPH grades. There was significantly greater overall expression of TNF-alpha mRNA at a high altitude; however, there was no difference within the various grades of EIPH. Expression of IL-10 was significantly affected by grade of EIPH because horses with grade 3 EIPH expressed significantly more IL-10 mRNA than did horses with grade 0 or 2 EIPH; this expression was not affected by location. CONCLUSIONS AND CLINICAL RELEVANCE: At sea level, increased IL-6 expression was associated with more severe EIPH, and altitude may affect gene expressions of the proinflammatory cytokine TNF-alpha and anti-inflammatory cytokine IL-6. Studies on protein concentrations of cytokine expression are needed. The pathophysiologic importance of these findings remains to be explained."

T0 Protein 594 605 interleukin
T1 Protein 660 694 tumor necrosis factor (TNF) -alpha
T2 Protein 774 793 IL-1 and INF-gamma
T3 Protein 852 862 IL-6 mRNA
T4 Protein 1165 1179 TNF-alpha mRNA
T5 Protein 1578 1582 IL-6
T6 Protein 1720 1729 TNF-alpha
T1096 Regulation 743 751
T1097 Gene_expression 758 768
T1098 Gene_expression 836 846
T1099 Gene_expression 913 922

T1100 Gene_expression 1150 1160
 T1101 Positive_regulation 1566 1575
 T1102 Gene_expression 1585 1595
 T1103 Regulation 1661 1667
 T1104 Gene_expression 1675 1686
 E222 Regulation:T1096 Theme:T2
 E223 Regulation:T1096 Theme:E224
 E224 Gene_expression:T1097 Theme:T2
 E225 Gene_expression:T1098 Theme:T3
 E226 Gene_expression:T1099 Theme:T3
 E227 Gene_expression:T1100 Theme:T4
 E228 Positive_regulation:T1101 Theme:T5
 E229 Positive_regulation:T1101 Theme:T6
 E230 Positive_regulation:T1101 Theme:E231
 E231 Gene_expression:T1102 Theme:T5
 E232 Gene_expression:T1102 Theme:T6
 E233 Regulation:T1103 Theme:T6
 E234 Gene_expression:T1104 Theme:T5
 E235 Gene_expression:T1104 Theme:T6

21983741 "[Association between diversity of hypoxia at different altitude and the polymorphism of EPAS1 gene]. OBJECTIVE: To study the selection effect of endothelial PAS domain protein 1 (EPAS1) gene induced by high altitude hypoxia environment. METHODS: Fourteen single nucleotide polymorphism sites (SNPs) of the EPAS1 gene were genotyped using PCR-restriction fragment length polymorphism (PCR-RFLP) in three Tibetan groups (58 samples from Tibetan living in an altitude of about 3700 meters above sea level, 47 from Qinghai province, about 3100 meters above sea level, 43 from Yunnan province, about 2500 meters above sea level), and Han of Shandong (47 samples, about 50 meters above sea level). RESULTS: There were significant differences of most SNP allelic, genotypic and haplotypic frequencies when comparing Han of Shandong, Tibetan of Yunnan with Tibetan of Tibetan and Qinghai. But no difference between Han of Shandong and Tibetan of Yunnan was found. CONCLUSION: The EPAS1 gene might be under hypoxic selection induced by high altitude."

T0 Protein 174 204 PAS domain protein 1 (EPAS1
 T1 Protein 331 342 EPAS1 gene
 T2 Protein 1014 1025 EPAS1 gene
 T1009 Positive_regulation 212 219

A46 Source E10 Current
A47 KT E10 Gen-Other
A48 CL E10 L3
A49 Manner E10 Neutral
A50 Polarity E10 Positive
E10 Positive_regulation:T1009 Theme:T0

22981402 "Naringenin and quercetin reverse the effect of hypobaric hypoxia and elicit neuroprotective response in the murine model. Exposure to high-altitude results in hypobaric hypoxia which is considered as an acute physiological stress. This condition often leads to high-altitude illnesses such as high-altitude cerebral edema, high altitude pulmonary edema and hypoxic muscle weakness. Hypoxic injuries can be prevented by either preconditioning with cobalt chloride or treatment with drugs. The aim of current investigation was to evaluate the effect of naringenin (NGEN) and quercetin (QUR) against behavioral impairment and neuronal damage in hypoxia induced murine model. An oral administration of NGEN or QUR (10mg/kg each) was given to the animal prior to every hypoxic treatment. Behavioral changes were evaluated along with the hypoxia exposure for all the groups. After hypoxia exposure and drug administration, the mice were euthanized; brains were harvested and stored for further analysis. Expressions of hypoxia induced proteins were ensured by Western blotting. Our results demonstrate expression of hypoxia inducible factor 1alpha (HIF1alpha), vascular endothelial growth factor (VEGF), active caspase 3 and ubiquitin levels were significantly reduced upon drug treatment. However, expressions of chaperones (Hsp70, Hsp90 and C-terminus Hsp70 interacting protein) were moderately changed. We established our findings based on behavioral test, hematoxylin and eosin as well as amino-cupric silver stainings. In addition, the protective nature of these drugs was corroborated with immunoblot and immunofluorescence results, where we confirmed the down regulation of caspase 3 and ubiquitinated proteins. To conclude, treatment with NGEN and QUR alone substantially ameliorated hypoxia induced brain dysfunction and acts like a neuroprotectant."

T0 Protein 1166 1210 hypoxia inducible factor 1alpha (HIF1alpha
T1 Protein 1213 1253 vascular endothelial growth factor (VEGF
T2 Protein 1281 1290 ubiquitin
T3 Protein 1398 1447 Hsp90 and C-terminus Hsp70 interacting protein
T4 Protein 1756 1765 caspase 3
T1118 Gene_expression 1151 1161
T1119 Gene_expression 1362 1373
T1120 Negative_regulation 1740 1750
E252 Gene_expression:T1118 Theme:T0
E253 Gene_expression:T1118 Theme:T1
E254 Gene_expression:T1118 Theme:T2
E255 Gene_expression:T1119 Theme:T3

21973220 "CYBA and GSTP1 variants associate with oxidative stress under hypobaric hypoxia as observed in high-altitude pulmonary oedema. HAPE (high-altitude pulmonary oedema) is characterized by pulmonary hypertension, vasoconstriction and an imbalance in oxygen-sensing redox switches. Excess ROS (reactive oxygen species) contribute to endothelial damage under hypobaric hypoxia, hence the oxidative-stress-related genes CYBA (cytochrome b-245 alpha polypeptide) and GSTP1 (glutathione transferase Pi 1) are potential candidate genes for HAPE. In the present study, we investigated the polymorphisms -930A/G and H72Y (C/T) of CYBA and I105V (A/G) and A114V (C/T) of GSTP1, individually and in combination, in 150 HAPE-p (HAPE patients), 180 HAPE-r (HAPE-resistant lowland natives) and 180 HLs (healthy highland natives). 8-Iso-PGF2alpha (8-iso-prostaglandin F2alpha) levels were determined in plasma and were correlated with individual alleles, genotype, haplotype and gene-gene interactions. The relative expression of CYBA and GSTP1 were determined in peripheral blood leucocytes. The genotype distribution of -930A/G, H72Y (C/T) and I105V (A/G) differed significantly in HAPE-p compared with HAPE-r and HLs ($P \leq 0.01$). The haplotypes G-C of -930A/G and H72Y (C/T) in CYBA and G-C and G-T of I105V (A/G) and A114V (C/T) in GSTP1 were over-represented in HAPE-p; in contrast, haplotypes A-T of -930A/G and H72Y (C/T) in CYBA and A-C of I105V (A/G) and A114V (C/T) in GSTP1 were over-represented in HAPE-r and HLs. 8-Iso-PGF2alpha levels were significantly higher in HAPE-p and in HLs than in HAPE-r ($P=2.2 \times 10^{-16}$ and 1.2×10^{-14} respectively) and the expression of CYBA and GSTP1 varied differentially ($P < 0.05$). Regression analysis showed that the risk alleles G, C, G and T of -930A/G, H72Y (C/T), I105V (A/G) and A114V (C/T) were associated with increased 8-iso-PGF2alpha levels ($P < 0.05$). Interaction between the two genes revealed over-representation of most of the risk-allele-associated genotype combinations in HAPE-p and protective-allele-associated genotype combinations in HLs. In conclusion, the risk alleles of CYBA and GSTP1, their haplotypes and gene-gene interactions are associated with imbalanced oxidative stress and, thereby, with high-altitude adaptation and mal-adaptation."

T0 Protein 20 35 GSTP1 variants
T1 Protein 445 479 cytochrome b-245 alpha polypeptide
T2 Protein 486 522 GSTP1 (glutathione transferase Pi 1
T3 Protein 698 703 GSTP1
T4 Protein 1576 1591 8-Iso-PGF2alpha
T1121 Binding 37 46
E257 Binding:T1121 Theme:T0

21232181 "Endothelial nitric oxide synthase gene polymorphisms associated with susceptibility to high altitude pulmonary edema in Chinese railway construction workers at Qinghai-Tibet over 4 500 meters above sea level. OBJECTIVE: To examine whether the polymorphisms of endothelial nitric oxide synthase (eNOS) gene are associated with the susceptibility to high altitude pulmonary edema (HAPE) in Chinese railway construction workers at Qinghai-Tibet where the altitude is over 4 500 m above sea level. METHODS: A case-control study was conducted including 149 HAPE patients in the construction workers and 160 healthy controls randomly recruited from their co-workers, matching the patients in

ethnicity, age, sex, lifestyle, and working conditions. Three polymorphisms of eNOS gene, T-786C in promoter, 894G/T in exon 7, and 27bp variable number tandem repeat (VNTR) in intron 4, were genotyped using polymerase chain reaction (PCR) and confirmed with DNA sequencing. RESULTS: The frequencies of 894T allele and heterozygous G/T of the 894G/T variant were significantly higher in HAPE patients group than in the control group ($P=0.0028$ and $P=0.0047$, respectively). However, the frequencies of the T-786C in promoter and the 27bp VNTR in intron 4 were not significantly different between the two groups. Haplotypic analysis revealed that the frequencies of two haplotypes (H3, T-T-b, b indicates 5 repeats of 27 bp VNTR; H6, C-G-a, a indicates 4 repeats of 27 bp VNTR) were significantly higher in HAPE patients (both $P<0.0001$). On the contrary, the frequencies of H1 (T-G-b) and H2 (T-G-a) were lower in HAPE patients than in healthy controls (both $P<0.001$). CONCLUSIONS: Two haplotypes (T-T-b and C-G-a) may be strongly associated with susceptibility to HAPE. Compared with the individual alleles of eNOS gene, the interaction of multiple genetic markers within a haplotype may be a major determinant for the susceptibility to HAPE."

T0 Protein 294 327 nitric oxide synthase (eNOS) gene

T1 Protein 807 816 eNOS gene

T2 Protein 1865 1874 eNOS gene

T3 Protein 2000 2006 HAPE . "

T1127 Binding 335 345

T1128 Binding 1881 1892

E263 Binding:T1127 Theme:T0

E264 Binding:T1128 Theme:T2 Theme2:T3

E265 Binding:T1128 Theme:T3 Theme2:T2

22568566 "KGF-2 targets alveolar epithelia and capillary endothelia to reduce high altitude pulmonary oedema in rats. High altitude pulmonary oedema (HAPE) severely affects non-acclimatized individuals and is characterized by alveolar flooding with protein-rich oedema as a consequence of blood-gas barrier disruption. Limited choice for prophylactic treatment warrants effective therapy against HAPE. Keratinocyte growth factor-2 (KGF-2) has shown efficiency in preventing alveolar epithelial cell DNA damages in vitro. In the current study, the effects of KGF-2 intratracheal instillation on mortality, lung liquid balance and lung histology were evaluated in our previously developed rat model of HAPE. We found that pre-treatment with KGF-2 (5 mg/kg) significantly decreased mortality, improved oxygenation and reduced lung wet-to-dry weight ratio by preventing alveolar-capillary barrier disruption demonstrated by histological examination and increasing alveolar fluid clearance up to 150%. In addition, KGF-2 significantly inhibited decrease of transendothelial permeability after exposure to hypoxia, accompanied by a 10-fold increase of Akt activity and inhibited apoptosis in human pulmonary microvascular endothelial cells, demonstrating attenuated endothelial apoptosis might contribute to reduction of endothelial permeability. These results showed the efficacy of KGF-2 on inhibition of endothelial cell apoptosis, preservation of alveolar-capillary barrier integrity and promotion of pulmonary oedema absorption in HAPE. Thus, KGF-2 may represent a potential drug candidate for the prevention of HAPE."

T0 Protein 420 448 Keratinocyte growth factor-2
T1 Protein 1614 1619 KGF-2
T2 Protein 1693 1699 HAPE . "
T1136 Negative_regulation 1678 1688
E290 Negative_regulation:T1136 Cause:T1 Theme:T2

20956315 "EGLN1 involvement in high-altitude adaptation revealed through genetic analysis of extreme constitution types defined in Ayurveda. It is being realized that identification of subgroups within normal controls corresponding to contrasting disease susceptibility is likely to lead to more effective predictive marker discovery. We have previously used the Ayurvedic concept of Prakriti, which relates to phenotypic differences in normal individuals, including response to external environment as well as susceptibility to diseases, to explore molecular differences between three contrasting Prakriti types: Vata, Pitta, and Kapha. EGLN1 was one among 251 differentially expressed genes between the Prakriti types. In the present study, we report a link between high-altitude adaptation and common variations rs479200 (C/T) and rs480902 (T/C) in the EGLN1 gene. Furthermore, the TT genotype of rs479200, which was more frequent in Kapha types and correlated with higher expression of EGLN1, was associated with patients suffering from high-altitude pulmonary edema, whereas it was present at a significantly lower frequency in Pitta and nearly absent in natives of high altitude. Analysis of Human Genome Diversity Panel-Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) and Indian Genome Variation Consortium panels showed that disparate genetic lineages at high altitudes share the same ancestral allele (T) of rs480902 that is overrepresented in Pitta and positively correlated with altitude globally ($P < 0.001$), including in India. Thus, EGLN1 polymorphisms are associated with high-altitude adaptation, and a genotype rare in highlanders but overrepresented in a subgroup of normal lowlanders discernable by Ayurveda may confer increased risk for high-altitude pulmonary edema."

T0 Protein 667 672 EGLN1
T1 Protein 895 906 EGLN1 gene
T2 Protein 1040 1045 EGLN1
T3 Protein 1625 1630 EGLN1
T1137 Gene_expression 1025 1035
E291 Gene_expression:T1137 Theme:T2
E292 Gene_expression:T1137 Theme:T1

22472608 "Neuroglobin regulates hypoxic response of neuronal cells through Hif-1alpha- and Nrf2-mediated mechanism. Oxygen sensing in hypoxic neurons has been classically attributed to cytochrome c oxidase and prolyl-4-hydroxylases and involves stabilization of transcription factors, hypoxia-inducible factor-1alpha (Hif-1alpha) and nuclear factor erythroid 2-related factor 2 (Nrf2) that mediate survival responses. On the contrary, release of cytochrome c into the cytosol during hypoxic stress triggers apoptosis in neuronal cells. We, here advocate that the redox state of neuroglobin (Ngb) could regulate both Hif-1alpha and Nrf2 stabilization and cytochrome c release during hypoxia. The hippocampal

regions showing higher expression of Ngb were less susceptible to global hypoxia-mediated neurodegeneration. During normoxia, Ngb maintained cytochrome c in the reduced state and prevented its release from mitochondria by using cellular antioxidants. Greater turnover of oxidized cytochrome c and increased utilization of cellular antioxidants during acute hypoxia altered cellular redox status and stabilized Hif-1alpha and Nrf2 through Ngb-mediated mechanism. Chronic hypoxia, however, resulted in oxidation and degradation of Ngb, accumulation of ferric ions and release of cytochrome c that triggered apoptosis. Administration of N-acetyl-cysteine during hypoxic conditions improved neuronal survival by preventing Ngb oxidation and degradation. Taken together, these results establish a role for Ngb in regulating both the survival and apoptotic mechanisms associated with hypoxia."

T0 Protein 191 237 cytochrome c oxidase and prolyl-4-hydroxylases

T1 Protein 297 340 hypoxia-inducible factor-1alpha (Hif-1alpha

T2 Protein 346 389 nuclear factor erythroid 2-related factor 2

T3 Protein 605 616 neuroglobin

T4 Protein 648 658 Hif-1alpha

T1147 Localization 702 709

E315 Localization:T1147 Theme:T3

E316 Localization:T1147 Theme:T4

23956087 "[Association between six single nucleotide polymorphisms of EGLN1 gene and adaptation to high-altitude hypoxia]. To investigate the association between SNPs located in 5'UTR and intron of prolyl hydroxylase 2 (EGLN1 or PHD2) and adaptation to high-altitude hypoxia, the SNPs (rs2066140, rs2808584, rs2491405, rs2486741, rs2486734 and rs21533646) of EGLN1 gene were genotyped using Sequenom MassArray genotyping system in 152 unrelated healthy Tibetan individuals (3 650 m altitude) and 192 Han (5 00 m altitude), and the haplotypes of these SNPs were constructed and analyzed. Our results showed all the homozygous genotypes of six SNPs loci were significantly different between the two groups ($P<0.05$). The frequencies of haplotypes G-G (rs2066140 and rs2808584) and G-C (rs2486741 and rs2486734) of high-altitude group were significantly different from low-altitude group ($P<0.05$). In addition, the frequencies of haplotypes C-A (rs2066140 and rs2808584) and C-T (rs2486741 and rs2486734) of high-altitude group were significantly lower than those in low-altitude group ($P<0.05$). Our results indicate that the polymorphism of homozygous genotype in six SNPs and their haplotypes were associated with adaptation to high-altitude hypoxia."

T0 Protein 71 82 EGLN1 gene

T1 Protein 206 226 prolyl hydroxylase 2

T2 Protein 368 379 EGLN1 gene

T1148 Binding 147 158

E317 Binding:T1148 Theme:T1 Theme2:T2

E318 Binding:T1148 Theme:T2 Theme2:T1

23266757 "Evidence for involvement of uncoupling proteins in cerebral mitochondrial oxidative phosphorylation deficiency of rats exposed to 5,000 m high altitude. The present study aimed to investigate the change of proton leak and discuss the role of cerebral uncoupling proteins (UCPs) and its regulatory molecules non-esterified fatty acid (NEFA) in high altitude mitochondrial oxidative phosphorylation deficiency. The model group animals were exposed to acute high altitude hypoxia, and the mitochondrial respiration, protein leak, UCPs abundance/activity and cerebral NEFA concentration were measured. We found that in the model group, cerebral mitochondrial oxidative phosphorylation was severely impaired with decreased ST3 respiration rate and ATP pool. Proton leak kinetics curves demonstrated an increase in proton leak; GTP binding assay pointed out that total cerebral UCPs activity significantly increased; Q-PCR and western blot showed upregulated expression of UCP4 and UCP5. Moreover, cerebral NEFA concentration increased. In conclusion, UCPs mediated proton leak is closely related to cerebral mitochondria oxidative phosphorylation deficiency during acute high altitude hypoxia and NEFA is involved in this signaling pathway."

T0 Protein 1043 1047 UCP4
T1149 Positive_regulation 862 870
T1150 Gene_expression 1028 1038
E319 Positive_regulation:T1149 Theme:T0
E320 Gene_expression:T1150 Theme:T0

23710233 "Rhodiola crenulata Extract Alleviates Hypoxic Pulmonary Edema in Rats. Sudden exposure of nonacclimatized individuals to high altitude can easily lead to high altitude illnesses. High altitude pulmonary edema (HAPE) is the most lethal form of high altitude illness. The present study was designed to investigate the ability of Rhodiola crenulata extract (RCE), an herbal medicine traditionally used as an antiacute mountain sickness remedy, to attenuate hypoxia-induced pulmonary injury. Exposure of animals to hypobaric hypoxia led to a significant increase in pathological indicators for pulmonary edema, including the lung water content, disruption of the alveolar-capillary barrier, and protein-rich fluid in the lungs. In addition, hypobaric hypoxia also increased oxidative stress markers, including (ROS) production, (MDA) level, and (MPO) activity. Furthermore, overexpression of plasma (ET-1), (VEGF) in (BALF), and (HIF-1 alpha) in lung tissue was also found. However, pretreatment with RCE relieved the HAPE findings by curtailing all of the hypoxia-induced lung injury parameters. These findings suggest that RCE confers effective protection for maintaining the integrity of the alveolar-capillary barrier by alleviating the elevated ET-1 and VEGF levels; it does so by reducing hypoxia-induced oxidative stress. Our results offer substantial evidence to support arguments in favor of traditional applications of Rhodiola crenulata for antihigh altitude illness."

T0 Protein 960 971 HIF-1 alpha
T1 Protein 1304 1308 VEGF
T1159 Positive_regulation 1285 1293
E330 Positive_regulation:T1159 Theme:T1