Review Article

Pulmonary Circulation

Vascular homeostasis at high-altitude: role of genetic variants and transcription factors

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Abstract

High-altitude pulmonary edema occurs most frequently in non-acclimatized low landers on exposure to altitude $\geq$2500 m. High-altitude pulmonary edema is a complex condition that involves perturbation of signaling pathways in vasoconstrictors, vasodilators, anti-diuretics, and vascular growth factors. Genetic variations are instrumental in regulating these pathways and evidence is accumulating for a role of epigenetic modification in hypoxic responses. This review focuses on the crosstalk between high-altitude pulmonary edema-associated genetic variants and transcription factors, comparing high-altitude adapted and high-altitude pulmonary edema-afflicted subjects. This approach might ultimately yield biomarker information both to understand and to design therapies for high-altitude adaptation.

Keywords

genetics, epigenetics, high-altitude adaptation

Date received: 10 December 2019; accepted: 14 February 2020

Pulmonary Circulation 2020; 10(4) 1–11
DOI: 10.1177/2045894020913475

Evolution and physiological adaptation have permitted survival at the highest topographically elevated regions of the world.[1–5] Reduced air pressure at high-altitude decreases the partial pressure of inspired oxygen, affecting lungs, brain, heart, and blood and can lead to a spectrum of high-altitude disorders including high-altitude pulmonary edema (HAPE), acute mountain sickness, and high-altitude cerebral edema.[6,7] This review focuses on HAPE. HAPE is a consequence of hypoxic pulmonary vasoconstriction leading to increased pulmonary arterial pressure and capillary stress failure.[8–11] HAPE victims have lower arterial oxygen saturation (SaO_2) and higher heart rate, pulmonary vascular resistance, and pulmonary vascular resistance index[12,13] than do unaffected sojourners to altitude. Clinically, HAPE is characterized by dyspnea, elevated body temperature, pink frothy sputum, tachypnea, tachycardia, persistent cough, and cyanosis.[14–17] Chest X-rays and CT scans show increased lung vascular markings and patchy shadows.[18,19] There have been great strides in understanding the clinical and physiological mechanisms of HAPE that has led to the discovery of successful treatments. Information on genetic contributions to this disorder has also grown rapidly over the last decade, partly to the development and implementation of newer genetic techniques.

Candidate gene approaches, advanced techniques such as Next-Generation Sequencing and Genome-Wide Association Studies have led to association of multiple genetic variants with high-altitude adaptation or maladaptation.[20–26] The majority of these genes belong to multiple, frequently related pathways. These include the renin–angiotensin–aldosterone system, apelin signaling, nitric oxide (NO) signaling, and hypoxia-induced signaling.

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These pathways regulate vasoactive molecules including angiotensin II (ANG II), apelin, NO, aldosterone, and beta-adrenergics.[27–31] In addition to genetic variation, epigenetics plays prominent role in HAPE and other diseases.[32–35] DNA methylation, acetylation, histone modifications/chromatin remodeling, and post translational RNA regulations are increasingly being recognized as mediators of crosstalk between genes and environment[36,37] paving the way to epigenetic-based therapeutics.[38,39] Interestingly, the Encyclopedia of DNA elements project consortium has mapped active transcription sites with an aim to identify the functional elements in the human genome.[40] Genetic variants that alter the binding site of transcription factors (TFs) are increasingly being identified and are associated with epigenetics.[41,42] It is now known that most of the genome is likely regulatory, and TFs play a crucial role in its recognition and defining the function that may again be in favor or against normal physiological signaling.[43] It is here that the relevance of TFs in diseases becomes integral. In fact, last few years have seen increasing efforts being put in to understanding the TF-mediated gene regulatory mechanisms. These efforts also highlighted the synchronization between the TFs and methylation; a synchronization that works in tandem to regulate and define a function.[35,44] Altered TF binding results in differential gene expression which brings out phenotypic differences in associated diseases.[35,45,46] This review will attempt to integrate genetics, TFs, and the molecular regulation of vascular homeostasis in HAPE. We first summarize the signaling pathways, the associated genetic variants, and the signaling molecules, followed by allele-specific transcriptional regulation by TFs. The overall purpose is to highlight the cellular crosstalk between HAPE-associated genetic variants and the TFs. We expect this will ultimately lead to biomarker identification and to focus on development of improved therapeutics.

Renin–angiotensin–aldosterone system-mediated allele-specific TF binding and salt sensitivity contribute to vascular dysfunction

The renin–angiotensin–aldosterone system (RAAS) involves renin-mediated conversion of angiotensinogen (AGT) to a decapeptide, angiotensin I (Fig. 1). The latter is converted into the vasoconstrictive, octapeptide ANG II by angiotensin-1 converting enzyme (ACE). In addition to vasoconstriction, ANG II, through the ANG II receptor (AGTR1), stimulates the adrenal cortex to secrete aldosterone, a major minerlocorticoid hormone, under the regulation of aldosterone synthase enzyme. Aldosterone acts on the

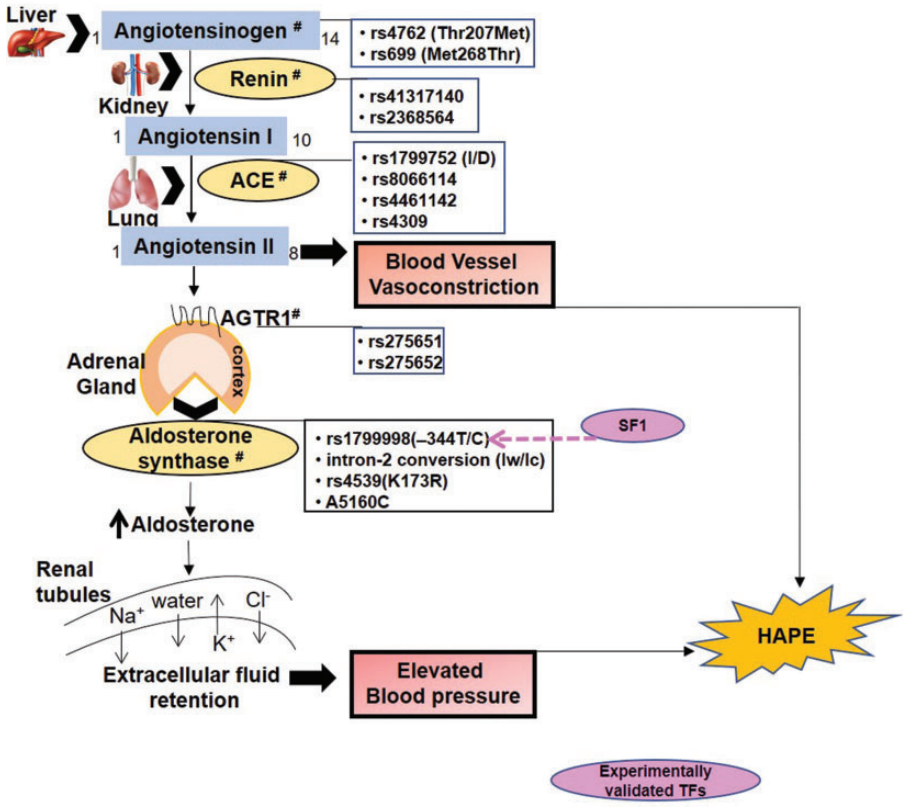

Fig. 1. The renin–angiotensin–aldosterone pathway regulates blood pressure and electrolyte balance in the body. ACE: angiotensin-1 converting enzyme; AGTR1: angiotensin II receptor; SF1: steroidogenic transcription factor. Note: Hash (#) represents HAPE-associated genetic variants.

mineralocorticoid receptors on the renal duct cells to increase the extracellular fluid retention via sodium chloride reabsorption and acts as an anti-diuretic, thereby regulating blood pressure and blood volume.[47,48]

Disturbance of the RAAS is attributed, in part, to genetic variants in at least five critical genes namely *REN, AGT*, ACE, *AGTR1*, and *CYP11B2*.[20,49–53] Of these, the major genetic variants that have been associated with HAPE are rs4762 (Thr207Met) and rs699 (Met268Thr) of *AGT*,[53,54] the insertion/deletion (indel) alleles (I/D, 287bp alu repeat sequence), rs8066114 and rs4461142 of *ACE*,[20,50,51,53,55] rs275651 and rs275652 of *AGTR1*,[56] and –344T/C and intron 2 conversion of *CYP11B2* (Fig. 1 and Table 1).[48,57] Whereas in case of the healthy native population, the homozygotes of major alleles of these genes such as the homozygotes rs4762CC of *AGT*, I/I of *ACE1*,[20,58] and –344TT of *CYP11B2*[48] were associated with HA adaptation, but not without conflicts especially on *ACE1* I/D

Table 1. Distribution of few significant SNPs in healthy controls and patients of HAPE.

				P-Value			
S no.	Gene	rs ID	Allele	HAPE-p vs HAPE-f	HAPE-p vs HL	HL vs HAPE-f	Significant genetic models
1	*AGT*	rs699[55]	A/G	0.05	–	–	Co-dominant and additive model
		rs4762[56]	G/A	–	0.024	0.03	Co-dominant and additive model
2	*ACE*	I/D[20,50,53]	I/D	≤0.05	–	–	Co-dominant and additive model
		rs8066114[57]	C/G	0.04; 0.03	–	–	Additive model; Dominant model
		rs4461142[57]	T/C	0.03	–	–	Dominant model
3	*AGTR1*	rs275651[56]	T/A	0.017	–	–	Additive model
		rs275652[56]	T/G	0.016	–	–	Additive model
4.	*CYP11B2*	–344T/C[48]	T/C	–	–	<0.0001	Additive model
		intron 2 conversion[57]	intron 2 conversion	–	0.03	–	Co-dominant model
5	*APLN*	*rs3761581*[25]	T/G	0.0027	3.9E-05	–	Co-dominant and additive model
		rs2235312[25]	C/T	1.0E-06	1.2E-06	–	Co-dominant and additive model
		rs3115757[25]	C/G	0.0032	0.04	–	Co-dominant and additive model
6	*APLNR*	rs11544374[25]	G/A	0.004	–	–	Co-dominant and additive model
		rs2282623[25]	A/G	0.013	1.0E-07	4.5E-05	Co-dominant and additive model
7	*NOS3*	rs1799983[21,25,80]	G/T	0.03	1.2E-05	–	Co-dominant and additive model
		rs7830[25]	A/C	1.6E-05	3.0E-06	–	Co-dominant and additive model
		4b/4a[21,25,80]	b/a	0.0003	9.0E-07	–	Co-dominant and additive model
	Gene	rs ID	Allele	Minor allele predominance			
8	*EPAS1*	rs56721780[104]	G/C	Absence of minor allele C in other world population except Tibetans			
		rs13419896[105]	G/A	Predominance of A allele in Tibetans and Sherpas			
		rs149594770[106]	T/A	Absence of minor allele A in other world population except Tibetans			
9	*EGLN1*	rs186996510[107]	G/C	Absence of minor allele C in other world population except Tibetans			
		rs12097901[107]	C/G	Absence of minor allele G in other world population except Tibetans			
				P-Value HAPE-p vs HAPE-f			Significant genetic models
		rs1538664[45]	T/C	$P < 0.008$			Co-dominant and additive model
		rs479200[45]	G/A/C				
		rs2486729[45]	C/G/T				
		rs2790879[45]	A/C				
		rs480902[45]	T/C				
		rs2486736[45]	C/T				
		rs973252[45]	A/G				

HAPE-p: HAPE-patients; HAPE-f: HAPE-free controls; HL: high-landers.

polymorphism.[13,59] These allelic variations in health and disease are also substantiated with varied circulating levels of the respective protein or enzyme levels. For example, the variants associated with increased circulating levels; where ACE, aldosterone, and sodium levels were increased in HAPE patients.[20,50,60] Here, the D allele was associated with elevated activity of ACE; likewise, –344C allele of *CYP11B2* was associated with elevated levels of aldosterone. Interestingly, however, ethnicity-based differences were also observed for few of the genes but in sealand population, such as the *CYP11B2* –344T/C polymorphism associated with increased salt sensitivity in the Japanese,[61] as the subjects with TT genotype displayed inappropriately higher aldosterone levels and systolic blood pressure in response to high salt intake. In addition to high-altitude adaptation and maladaptation, RAAS genetic variants have been extensively investigated in hypertension and cardiovascular diseases.[52,62,63]

Variants of RAAS pathway are predicted to change the respective protein's physicochemical properties, secondary structure, and solvent accessibility, which in turn may affect the binding of a molecule with its target.[64] Under the given conditions, allele-specific binding of TFs may amend gene expression, leading to phenotypic differences in several diseases.[42,46] Of the several genetic variants of RAAS, the *CYP11B2* variant –344T/C appears significant because of its interaction with a TF, namely steroidogenic TF (SF1).[65] Stronger binding of SF1 to variant –344C, as confirmed by electrophoretic mobility shift assay (EMSA),[65] was associated with elevated aldosterone levels in HAPE and hypertension.[59,66] However, as conveyed already elsewhere above, this gene represents variations from population to populations, such as the T allele was also associated with SF1 factor and with high aldosterone levels and blood pressure.[67,68] Such conflicts were attributed to sampling and genetic differences between the populations.[68] Under such circumstances, it is possible that a TF may strongly bind to one allele at a given locus but may also bind indirectly and weakly to other allele. Furthermore, at any given time more than one, TFs are attracted to a particular allelic locus,[35,69,70] though due to specificity, only one TF will bind to the allelic locus and other TFs will hang along the first TF.[45] Likewise, altered binding of p300, a histone acetyl transferase and HDACs, a histone deacetylase at *ACE* I/D polymorphism may control ACE levels by differentially regulating histone acetylation and deacetylation.[71] It is vital to note that most TFs do not work alone, instead these form homotypic and heterotypic interactions. Such interactions, which are abundant in the system, comprise of TF–TF, TF–nucleosome, and such other combinations. Thus, there are ways to interact and collaborate, such as the cooperative binding and the synergistic regulation. Now, these combinations/attractions could be dimeric, trimeric, and higher-order.[72] It also defines the various types or classes of TFs and thereby the mechanisms that have been so very well elucidated in recent times. However, it is not the intention of this review to interpret these interactions. It is pretty obvious from these findings that physiological traits are vulnerable to the complex human system.

Allele-dependent control of apelin and NO signaling

G-protein-coupled apelin receptors (APJ) and NO signaling play crucial role in maintaining pulmonary vascular homeostasis.[25,73] Its malfunction is associated with several diseases including HAPE, pulmonary arterial hypertension, and cardiovascular diseases.[25,74] X-linked apelin (*APLN*) gene encodes different variants of apelin peptide, differing in number of amino acid residues (apelin-36, -31, -28, -13), which upon binding to the vascular endothelial APJ possesses hypotensive as well as angiogenic activity (Fig. 2). Apelin phosphorylates serine/threonine-specific protein kinase B (Akt), raises intracellular calcium levels, and facilitates the production of NO, a potent vasodilator, generated by the endothelial NO synthase (NOS3) protein.[57] Apelin-mediated angiogenesis is a consequence of its phosphorylation (ERKs and Akt), leading to the proliferation of endothelial cells and the formation of new blood vessels.[75] Apelin also mediates vasoconstriction by stimulating myosin light chain phosphorylation in vascular smooth muscle cells.[76]

Interestingly, the expression of *Apelin* and *NOS3* as well as circulating levels of apelin 13 and NO when downregulated contribute to impaired vasodilation in HAPE patients.[25] This decrease in the levels of vasodilators was associated with several genetic variants such as *Apelin* rs3761581, rs2235312, and rs3115757; apelin receptor (*APLNR*) rs11544374 and rs2282623; and *NOS3* rs1799983, 4b/4a, and rs7830 (Fig. 2 and Table 1). The apelin–APJ polymorphisms also were reported with low apelin 13 levels and the risk of hypertension.[77] The risk alleles include *Apelin* rs3115757C, rs56204867C, and rs3761581A.[78] Beside polymorphisms, in vitro functional assays viz luciferase assay and real-time PCR, revealed allele-specific transcriptional regulation of apelin/APJ pathway by TFs such as TF specificity protein 1 (SP1).[79] Likewise, electrophoretic mobility shift assay and chromatin immunoprecipitation confirmed SP1 binding to the *APLNR* polymorphism rs9943582 (–154G/A), specifically to G allele and thereby upregulating its expression. In addition to APLNR, apelin is also a direct transcriptional target of SP1 (Fig. 2). Thus, transcriptional upregulation of both, *Apelin* and *APLNR*, in response to SP1 enhances apelin–APJ signaling. This relates to blood pressure disorder, progression of atherosclerosis, and increased susceptibility to brain infarction.[79] Interestingly, of the several TFs, SP1, signal transducer and activator of transcription 3 (STAT3), and Activating transcription factor 4 (ATF4) are known to control transcriptional regulation of apelin and APLNR.[80,81]

NOS has three isoforms, two constitutive, i.e. neuronal (NOS1) and endothelial (NOS3), and one inducible (NOS2), and all isoforms produce NO, which promotes cyclic

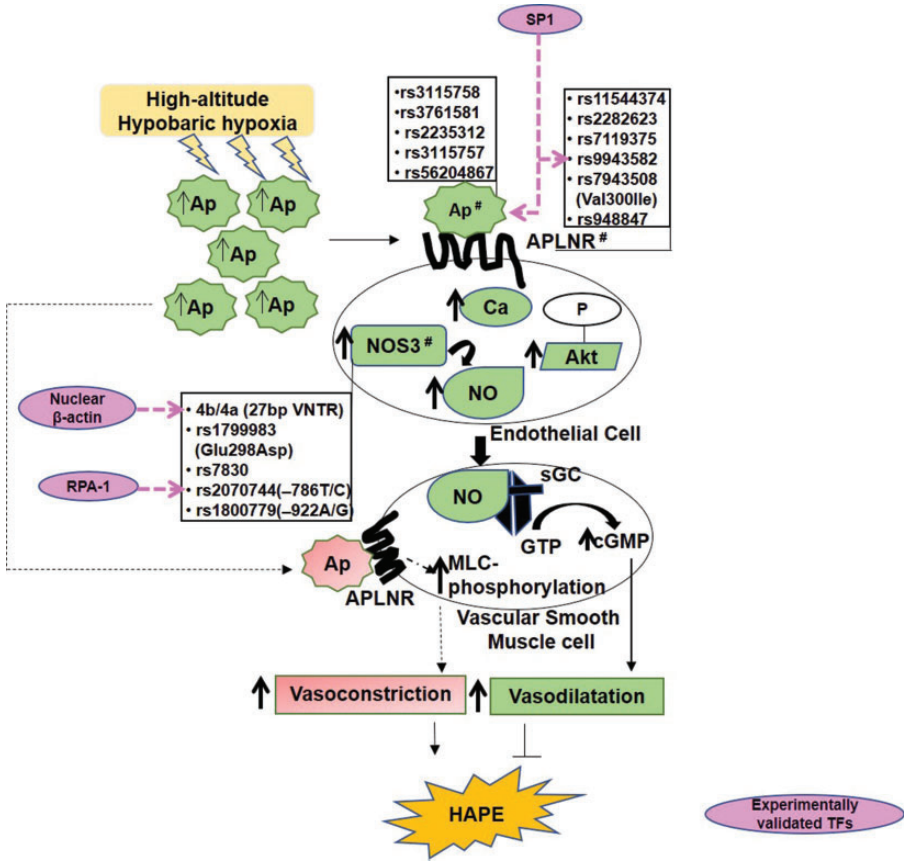

Fig. 2. The apelin and nitric oxide signaling system. Apelin mediates nitric oxide-mediated smooth muscle relaxation via Akt and calcium signaling (Solid lines). Apelin mediates vascular smooth muscle cells contraction via myosin light chain (MLC) phosphorylations (dashed lines).
Ap: Apelin; APLNR: Apelin receptor; Ca: calcium; NOS3: nitric oxide synthase; NO: nitric oxide; sGC: soluble guanylate cyclase; GTP: guanosine triphosphate; cGMP: cyclic guanosine monophosphate; SP1: specificity protein 1; RPA1: replication protein 1; VNTR: variable number tandem repeat; MLC: myosin light chain; HAPE: high-altitude pulmonary edema; TF: transcription factor.
Note: Hash (#) represents HAPE-associated genetic variants.

guanosine monophosphate-mediated vascular smooth muscle relaxation by activating guanylate cyclase.[21,27] Differential NO levels were associated with *NOS3* polymorphism at high-altitude.[21,82,83] Low NO levels were associated with haplotype of *NOS3* bearing heterozygotes, i.e. GTbaAGTC of the polymorphisms 894G/T, 4b/4a (27bp repeat), –922A/G and –786T/C in HAPE patients, while the homozygous haplotype GG/bb of G894T and 4b/4a polymorphisms was associated with elevated NO levels in HA natives.[21,25,61,81,83] Three *NOS3* polymorphisms namely 894G/T, 4b/4a, and –786T/C are the most studied and validated (Fig. 2). Beginning with rs1799983 (894G/T), it encodes protease-sensitive *NOS3* Glu298Asp variant (894T) that associates with decreased NO levels in HAPE patients.[25,82,84,85] The reduced levels of NO in turn cause hypoxia-mediated pulmonary vasoconstriction[72,86] and are inversely related to increased levels of an endogenous NOS inhibitor, asymmetric dimethylarginine.[87] On the contrary, the 894G allele associates with increased NO levels and adaptation and acclimatization in several different high-altitude populations like the Ladhakis, the Chinese from Qinghai-China, the Han recruits traveling to the Lhasa plateau, and the Quechua of the Andean population.[25,82,83] Likewise, the *NOS3* 4b/4a intron 4 variant that expresses five or four copies of the 27bp variable number tandem repeat is pertinent. The 4b allele associates with elevated NO levels and *NOS3* expression in high-altitude adaptation,[82] while the 4a allele associates with low NO and *NOS3* expression in HAPE and hypertension.[21,88] Of the several nuclear TFs bound to 27bp repeats as revealed through biotin–streptavidin pull down assay, mass spectrometry, and luciferase reporter assay,[89] β-actin (Fig. 2) upregulated NOS3 expression in the presence of 4b allele.[90] With β-actin's specificity for 27bp repeats and its role in the associated NOS3 transcriptional regulation, perhaps β-actin works here like a TF.

On the contrary, in vitro studies such as northern blot showed endothelial cells with 4b allele displayed higher levels of a 27bp small interference RNA, leading to decreased *NOS3* expression compared to the 4a allele.[91] In case of the *NOS3* –786T/C promoter polymorphism, the protective –786T allele enhances *NOS3* transcription efficiency as compared to its risk –786C allele;[89] whereas, specific binding of replication protein A1 to its risk –786C allele

decreased *NOS3* transcription.[92] This could be related to risk –786C allele-dependent decreased NO levels in HA adaptation. Surprisingly, in relation to –786T/C polymorphism, 4b/4a plays a contrasting cis-acting role in *NOS3* regulation. Here, both the protective 4b and risk 4a alleles decreased the *NOS3* transcription efficiency in the presence of the protective –786T allele.[89] On the other hand, both the 4b and 4a alleles increased the *NOS3* transcription efficiency in the presence of the risk C allele of *NOS3* –786T/C promoter polymorphism. This could be attributed to the various TFs that are attracted to these allele-specific sites (Fig. 2).

Differential expression of the hypoxia-inducible factor-signaling in the presence of TFs

Expression and activity of hypoxia-inducible factor (HIF)-1, a key oxygen-sensitive TF, increases exponentially with decrease in cellular oxygen.[93,94] The HIF signaling is depicted in Fig. 3. HIF-1 consists of an oxygen-sensitive HIF-1α subunit and a constitutively expressed HIF-1β subunit. HIF-1 drives transcriptional activation of numerous genes involved in vascular homeostasis, erythropoiesis, angiogenesis, and glycolysis.[95,96] Although HIF-1α subunit shares 48% sequence homology with HIF-2α subunit (encoded by the endothelial Per/ARNT/Sim domain protein-1 (*EPAS-1*)) and both bind to the same consensus sequence, hypoxia response element, however, HIF1 and HIF2 mediate different responses to hypoxia.[97,98] Another molecule in this system, EGLN1, encoding prolyl hydroxylase 2 (PHD2), negatively regulates the activity of HIF-1α by hydroxylation of its two prolines.[97] Additionally, PHD2/HIF-2α axis regulates pulmonary arterial pressure in vivo by antagonistically regulating vasoconstrictor, Endothelin 1, and the vasodilator, apelin-mediated signaling.[99] However, which of the two molecules is activated more at any given time will depend on the overall pathways influenced. The expression of PHD2 is regulated under hypobaric environment.[45] Over the years, the polymorphisms in these genes have found relevance (Fig. 3 and Table 1).

Several independent groups have shown association of the polymorphisms in *EPAS1*/*HIF2α* and *EGLN1* with high-altitude adaptation in Tibetans.[100–103] Interestingly, two *EPAS1* promoter polymorphisms, rs56721780 and an indel positioned at –886 and –742 upstream of its TSS,

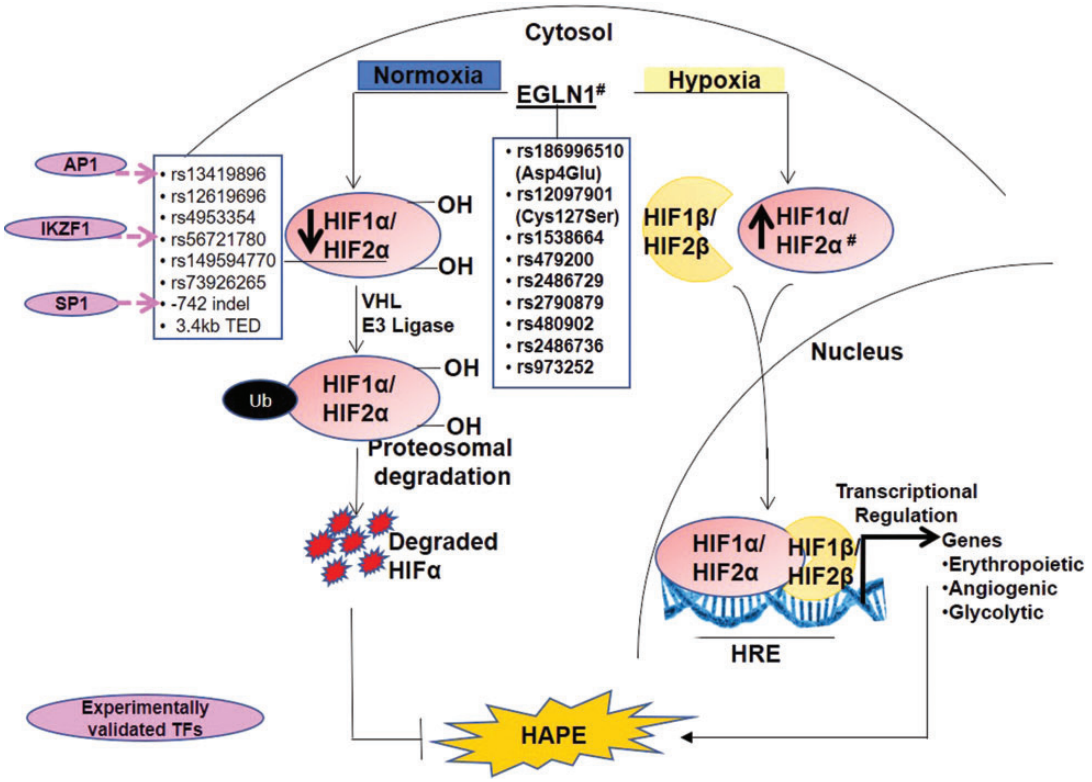

Fig. 3. The hypoxia signaling pathway involves EGLN1-mediated hydroxylation and VHL-dependent ubiquitination of HIF-1α/2α subunits leading to its proteosomal degrardation under normoxic conditions. However, under hypobaric hypoxic conditions, HIF-1α/2α subunits are stabilized, which complexes with HIF-β subunit and drives transcriptional regulation of numerous genes involved in vascular homeostasis.
HIF: hypoxia-inducible factor; HRE: hypoxia response element; VHL: Von Hippel-Lindau; Ub: ubiquitin; indel: insertion–deletion; 3.4kb TED: Tibetan-enriched 3.4kb deletion; D4E: aspartate4glutamate; C127S: cysteine127serine; IKZF1: IKAROS family zinc finger 1; SP1: specificity protein 1; AP1: activator protein 1; EGLN1: Egl nine homolog 1; HAPE: high-altitude pulmonary edema; TF: transcription factor.
Note: Hash (#) represents high-altitude adaptation/maladaptation associated genetic variants.

regulate *EPAS1* by allele-specific TF binding (Fig. 3). Here, the rs56721780C allele decreased the binding of *EPAS1* transcriptional repressor, IKAROS family zinc finger 1 as confirmed by EMSA. While the 40bp insertion at –742 indel increased the binding of its transcriptional activator SP1. Thus, both the rs56721780C allele and the –742 insertion increased *EPAS1* levels as revealed by luciferase reporter assays. This modification has been associated with higher birth weight and embryonic development in Tibetan newborns.[104] Similarly, another *EPAS1* polymorphism in intron 1, namely rs13419896, regulates *EPAS1* transcription.[105] The rs13419896A allele that was associated with high-altitude adaptation in Tibetans and Sherpas, has also been reported to bind to the TF Activator protein-1 (AP1) that upregulated the *EPAS1* levels. Contrary to this, evidence of diminished *EPAS1* activity at high-altitude has also been reported.[106] For example, another Tibetan-enriched *EPAS1* rs149594770A allele weakens its TF-binding capacity as well as its promoter activity as seen by EMSA and luciferase reporter assay.[106] This weakened *EPAS1* activity was attributed to the relatively low hemoglobin level in Tibetans.[100,106]

Among the other members of HIF signaling, *EGLN1* polymorphisms have been investigated (Fig. 3 and Table 1). Several *EGLN1* variants and its haplotypes are reported to associate with decreased SaO_2 levels, increased pulmonary arterial systolic pressure (PASP), and circulating *EGLN1* levels in HAPE.[45] Specifically, two key exonic polymorphisms, rs186996510 (Asp4Glu) and rs12097901 (Cys127Ser), contribute to high-altitude adaptation in Tibetans,[107] albeit at a lower frequency in highland Andeans.[108] Interestingly, these two missense variants exhibit low Km for oxygen and promote increased HIF-1α degradation under hypoxic conditions.[107] Abrogation of HIF-mediated responses like erythropoiesis prevents polycythemia in Tibetans. In fact, *EGLN1* gain-of-function mutants in combination with *EPAS1* polymorphisms also associated with decreased hemoglobin concentration in Tibetan highlanders.[109] Surprisingly, another study reported the *EGLN1* Tibetan haplotype, D4E/C127S, as loss-of-function mutant, which increases HIF-1α-mediated respiration and NO levels.[110] Although TFs have so far not been reported in regard to *EGLN1* variants, however, we have found few important TFs associating with *EGLN1* variants (unpublished). Therefore, altered binding of TFs to *EGLN1* variants (Fig. 3) may regulate HIF-signaling under the hypobaric hypoxic environment at high-altitude.

Gene to drug interactions in HAPE

Drug responses increasingly are being seen to be influenced by genetic polymorphisms. Nifedipine pharmacokinetics are influenced by genetic polymorphisms in *cytochrome P450*

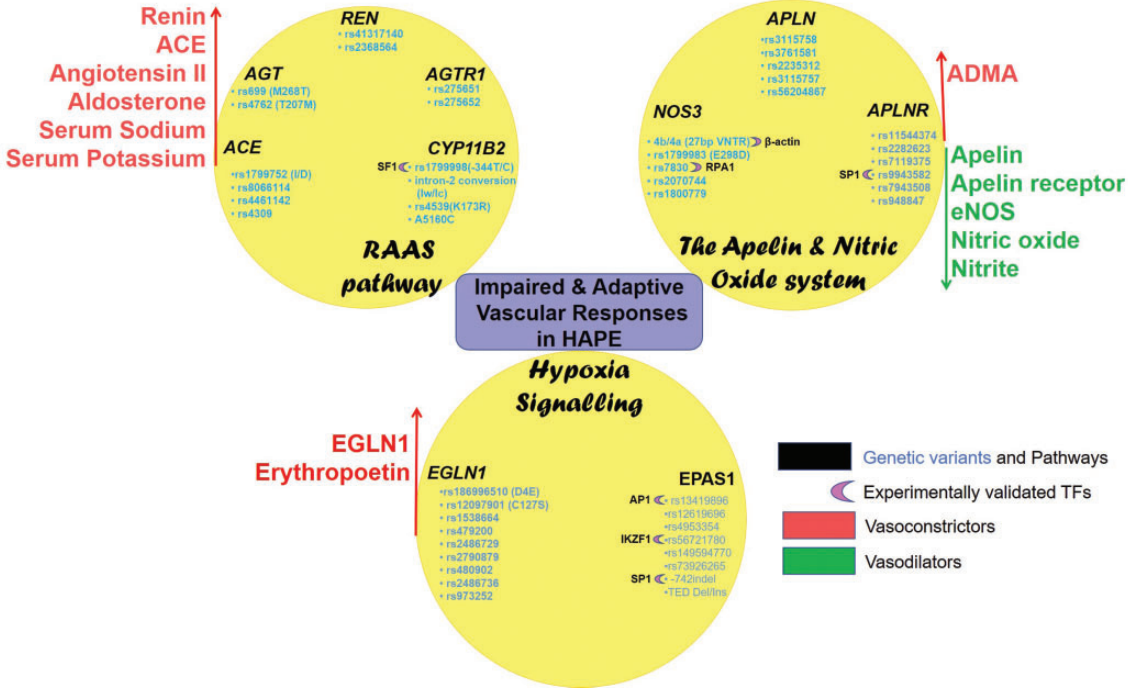

Fig. 4. Genetic variants and associated TFs in pathways of interest control vascular homeostasis by regulating the levels of vasodilators and vasoconstrictors.

Ren: renin; AGT: angiotensinogen; ACE: angiotensin converting enzyme; AGTR1: angiotensin receptor; CYP11B2: aldosterone synthase; SF1: steroidogenic transcription factor; APLN: apelin; APLNR: apelin receptor; NOS3: endothelial nitric oxide synthase; RPA1: replication protein A1; SP1: specificity protein 1; AP1: activator protein 1; ADMA: asymmetric dimethylarginine; EGLN1: Egl nine homolog 1; EPAS1: endothelial Per/ARNT/Sim domain protein-1; IKZF1: IKAROS family zinc finger 1; RAAS: Renin–angiotensin–aldosterone system.

(CYP) 3A5.[111] Sildenafil protects against the development of altitude-induced hypoxemia, pulmonary hypertension, and improves gas exchange.[112] Sildenafil response is influenced by *NOS3* genetic polymorphisms in several diseases including pulmonary hypertension.[113] The polymorphism in the β-adrenergic receptor 2 (*ADRB2)* gene affects therapeutic responses to beta agonists. The *ADRB2* Arg16Gly *loss-of-function* polymorphism in particular dictates responses in heart patients.[114] Renin polymorphisms predict the effects of thiazide diuretics, genetic variants in patients with decompensated heart influenced furosemide drug response.[115] While mineralocorticoid receptor gene variation influences dexamethasone-induced stress response.[116] Such insights from pharmacogenomics research will help to characterize genetic determinants effecting drug response to HAPE; paving way to personalized medicines. Of consequence, research on the role of TFs in influencing drug response is increasing.[117,118] For instance, one mechanism of action of aminophylline involves recruitment and activation of HDACs,[119] allele-specific HDACs binding to genetic variants may alter drug response in HAPE. Likewise, acetazolamide controls transcriptional activation of several TFs namely, AP-1, HIF, Heat shock factor (HSF), Nuclear factor-kappa B (NF-κB), Nuclear factor erythroid 2-related factor 2 (NRF2), Tumor suppresor p53 (p53), and STAT3.[120] Also, the corticosteroid action involves binding to several TFs including AP-1 or NF-κB as well recruitment of HDACs.[121] Thus, recent advances surely encourage to envisage equally greater role for the various TFs in conjunction with the genetic variants in shaping a physiological path.

Conclusion

We conclude that genetic variants and TFs play a pivotal role in the regulation of HAPE. Allele-specific binding of TFs seems to play a critical role in determining the causal role and may be contributed by select loci. This observation is an outcome of understanding of several of the pertinent physiological pathways. Evidences of cellular role of allele-specific TF binding in regulating these effects are wanting. As of now, none of the genetic marker has diagnostic potential, unless tested in a larger sample size. Investigations on association of genetic polymorphisms with predicted TFs under hypobaric hypoxic conditions would shed light on the physiological processes thereby advancing the development of diagnostics and therapeutics.

Future perspectives

In addition to genetics, epigenetic influences play a significant role in the regulation of physiological functions and human health. With newer information on disease-associated genetic variants, more extensive studies on polymorphisms-mediated changes in putative TF-binding motifs, chromatin structure, chromatin states, methylation, and gene expression will further elucidate the mechanisms underlying the disease. Additionally, pharmacogenomics research in turn will greatly enhance the life-expectancy or survival of the fittest under the given extreme environment.

Author contributions

N.C. contributed to designing the concept, writing, and correcting the manuscript. T.P. contributed the write-up and designing the figures. J.H.N. conceived, designed and supervised the project, contributed to writing, and correcting the manuscript. M.A.Q.P. conceived, designed and supervised the project, contributed to human sample collection, analyses, writing, and correcting the manuscript.

Acknowledgements

We thank the Director of CSIR-Institute of Genomics and Integrative Biology, Delhi, for the infrastructure.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Funding

This work is majorly supported by CSIR, India (grant numbers MLP1401 and BSC0123) and in part by CMREF, USA (grant number GAP0119) and ICMR (fellowship to NC. and EMS to Q.P., ref 74/6/2015-Pers/EMS).

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