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COMMENTARY

Hypertension at high altitude: the interplay between genetic and biochemical factors in the setting of oxidative stress

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Essential hypertension, which is a complex multifactorial syndrome and classic cardiovascular disease risk factor, contributes to adult morbidity and mortality worldwide each year. The physiological regulation of blood pressure (BP) is primarily dependent on the complex interactions between environmental and genetic factors. The past three decades have witnessed remarkable progress in the study of hypertension as a result of single-locus research and genome-wide association studies; however, the common predisposing genetic markers of the disease have yet to be established. The failure to identify the markers of hypertension may be the result of the smaller sample sizes used for the aforementioned association studies, the lack of replicated studies involving cohorts of either the same or different ethnicities, the lack of gene–gene interaction studies or the inappropriate selection of markers for the aforementioned association and interaction studies.

Oxidative stress (OS) is a multisystem phenomenon that is involved in the regulation of BP, and affects the heart, kidneys, nervous system, vasculature and immune system. Moreover, OS accompanied by decreased nitric oxide levels in the brain results in sympathoexcitation, which has an important role in the pathogenesis of hypertension.[1] The findings published by Kumar *et al.*[2] elegantly demonstrate the relationship between *CYBA* (p22phox) genetic variants and their haplotypes in the setting of essential hypertension in both high- and low-altitude populations. The selection of two populations in this study seems appropriate because hypertension results in more than seven million deaths every year; the incidence among lowlanders worldwide is increasing.[3,4] However, the epidemiological data regarding the prevalence of hypertension in lowlanders who reside temporarily at high altitudes or native highlanders who live under stressed conditions are scarce. Furthermore, given these extreme environmental conditions, the selection of candidate genes related to OS, such as *CYBA* (p22phox), also seems appropriate; however, the relationship between *CYBA* (p22phox) and hypertension has been questioned in previous studies.

There is evidence to suggest that OS has a central role in the progression of both clinical and experimental forms of hypertension.[5,6] OS results from increased production of reactive oxygen species and decreased levels of antioxidants, such as superoxide dismutase, catalase (CAT) and vitamins A, C and E, in the setting of hypertension. Recent studies have also suggested that altered renal CAT and glutathione peroxide mRNA expression and activity precede the development of hypertension in spontaneously hypertensive rats.[7] Kumar *et al.* demonstrated that the downregulation of CAT and the upregulation of 8-iso-prostaglandin F2α (8-isoPGF2α) may represent promising markers of oxidative injury among hypertensive individuals. Diminished CAT activity results in excessive reactive oxygen species production and elevated 8-isoPGF2α levels in these patients. The oxidant–antioxidant imbalance in hypertensive patients documented by Kumar *et al.* demonstrated a shift toward increased oxidant levels, a finding that is suggestive of its possible contribution to the pathogenesis of the disease. Of note, aberrant OS-mediated redox signaling causes inflammation, hypertrophy, apoptosis, migration, fibrosis, angiogenesis, endothelial dysfunction and severe vascular remodeling in the setting of hypertension.[8] Furthermore, the inter-individual susceptibility to hypertension and varied responses to targeted therapies may be explained by both genotype and phenotype correlations. Interestingly, Kumar *et al.* observed that an increased risk of hypertension exists among patients carrying the maximum number of risk alleles compared with patients carrying fewer numbers of risk alleles (Figure 1). However, the patients with protected alleles exhibited a reduced susceptibility to hypertension. The risk or protection conferred by individual alleles or haplotypes has a prominent role in both the functional and the molecular mechanisms underlying pathophysiology of the disease.[9,10] Furthermore, the hypertension associated risk haplotypes correlated with decreased CAT activity, increased 8-isoPGF2α levels, increased systolic BP, increased diastolic BP and increased mean arterial pressure. Conversely, the protective haplotypes were associated with increased CAT activity, decreased 8-isoPGF2α levels and decreased clinical parameters, highlighting the functional relevance of *CYBA* (p22phox) gene variants in hypertension.

The possible involvement of OS in the underlying pathology of the disease is not without controversy. There exists a large amount of evidence suggesting that OS may not be the causal mechanism of hypertension. In fact, it has been suggested that

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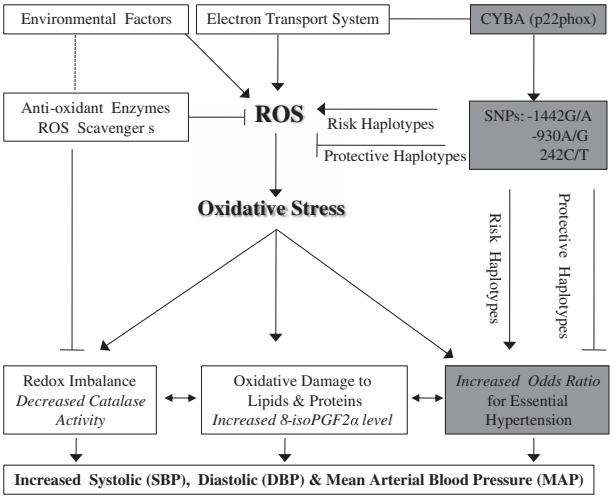

Figure 1 Diagrammatic representation for association of CYBA (p22phox) polymorphism with pathophysiology of essential hypertension. A full colour version of this figure is available online at the *Journal of Hypertension Research* website.

hypertension may cause OS.[11] Therefore, the possibility that OS is involved in the development of additional altitude related maladies is considerable. Conventional wisdom assumes the efficacy of 'antioxidant therapies' in counteracting high-altitude maladies. However, Julian *et al.*[12] recently questioned this hypothesis. They determined that hypobaric hypoxia-enhanced enzymatic antioxidant systems in subjects prone to acute mountain sickness. They proposed that quenching oxidant activity may exert adverse downstream effects. Whether such a phenomenon exists in the case of hypertension remains unknown.

In conclusion, the study by Kumar *et al.* may have added a new dimension to the study of hypertension, particularly at high altitudes; however, studies with larger sample sizes containing additional genetic variants are necessary to develop specific biomarkers and effective disease management strategies.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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