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Vascular Oxidation in Age-Related Hypertension: Benefits of Redox Equilibrium Restitution

Hilgers RH, Kundumani-Sridharan V, Subramani J, Chen LC, Cuello LG, Rusch NJ, et al. Thioredoxin reverses age-related hypertension by chronically improving vascular redox and restoring eNOS function. **Sci Transl Med. 2017;9(376). pii: eaaf6094. http://doi.org/cszs**

Aging is an independent risk factor for the development of hypertension and, as is well known, hypertension is a very important risk factor for the origin and progression of cardiovascular diseases. Thus, the association between increasing age, the progressive increase of blood pressure and the greater probability of suffering cardiovascular events, represents a multifactorial vicious circle that ends as one of the world's main causes of morbidity and mortality. A combination of biochemical processes contributes to hypertension in old age, such as oxidative stress, lack of nitric oxide, increased renin-angiotensin-aldosterone system activity and endothelial dysfunction. Patient studies demonstrated that stiffness of the great arteries is a relevant physiopathological process in the increase of systolic blood pressure. More recently, it has also been shown that the endothelial dysfunction of the great arteries and the microvasculature observed with aging favors the development of hypertension. Moreover, growing evidence suggests progressive impairment of nitric oxide bioavailability, a powerful vasodilator, thus increasing peripheral vascular resistance. In addition, nitric oxide synthesis deviation towards formation of free radicals, such as peroxynitrite, favors chronic oxidation of blood vessel proteins which, therefore, loose their relaxation capacity. The increase of age-related vascular oxidative stress is produced by greater generation of free radicals, but also due to their lower depuration. Thioredoxin (TRX), a protein which has been well studied during the last years, is associated with the maintenance of redox equilibrium. It eliminates free radicals, but has also great capacity, through its reductase properties, of converting oxidized proteins to their native state. At the experimental level, it has been shown that hypertensive animals have lower TRX expression and that its overexpression reverses a hypertensive phenotype to a normotensive one. However, the role of this protein in age-related hypertension had not been studied.

In this original and interesting work, Rob Hilgers et al. analyzed the physiopathological participation of TRX in age-related hypertension and its potential therapeutic uses. They observed that transgenic mice overexpressing TRX did not develop age-related hypertension compared with non-transgenic old mice or those which were dominant negative for this protein. These mice were able to remain normotensive thanks to the TRX ability of maintaining the vascular redox state in its reduced form, similar to young animals. It was also clearly shown that maintenance of oxidation/reduction equilibrium in aging blood vessels was due to different mechanisms associated with the functional protection of endothelial nitric oxide release, lower superoxide anion production and hence, the prevention of protein oxidation, which altogether resulted in the preservation of the peripheral vascular bed relaxation. A very significant finding of these experiments is that human-recombinant TRX administration to old hypertensive mice reversed blood pressure values to the normotensive levels of young animals. Moreover, although the administration of recombinant TRX was performed during three consecutive days, its effects were maintained during the three-week duration of the experimental protocol..

The multifactorial physiopathological nature of hypertension in the elderly, frequently forces a combined therapeutic management with different drugs that act on renal function, the renin-angiotensin-aldosterone system or the calcium channels. Although the benefits of these therapeutic strategies are unquestionable, especially on the reduction of the incidence of cardiovascular events, none of them offers healing options for a disease of rising prevalence in populations with growing age. This explains the great interest generated by the TRX protein, as it can not only eliminate excess free radicals, by also reverse oxidized proteins to their native functional form, generating longer benefits on the two main determinants of hypertension, increased vascular stiffness and loss of relaxation factors. In addition, it is no minor detail that free radicals seem to be the common denominator of these benefits, as ultimately, we live in a planet loaded with oxygen where we all grow old oxidizing.