Heal Thyself

Endogenous pathways of protection for oxidative stress

Kenneth Maiese*

Editor-in-Chief; Division of Cellular and Molecular Cerebral Ischemia; Departments of Neurology and Anatomy & Cell Biology; Barbara Ann Karmanos Cancer Institute; Center for Molecular Medicine and Genetics; Institute of Environmental Health Sciences; Wayne State University School of Medicine; Detroit, MI USA

As we continue to gain further insight of human biology, we learn that the body has remarkable promise and potential to defend itself from a number of disorders. For example, adipose derived stem cells have the uncanny ability to secrete soluble factors, such as macrophage colony stimulating factors, interleukins, and trophic factors to regulate immune system function and lead to new vessel growth and possible cardiac regeneration. In the olfactory neuro-epithelium, defense mechanisms exist to protect the central nervous system from the environment. The cells of the neuro-epithelium surprisingly can detoxify inhaled and blood circulating xenobiotics by metabolizing enzymes and using xenobiotic transporters. Internal systems, such as the gastrointestinal tract, employ the endogenous release of calcitonin gene-related peptide to prevent ulceration and also speed the recovery of healing. In addition, recent studies demonstrate that the body may release specific heat shock proteins, such as heat-shock protein 65, to provide protection against arthritis. Furthermore, agents that are commonly ascribed to one system of the body, such as the hematological system, may actually impart significant protection in tissue elsewhere in the body. A case in point is the growth factor and cytokine erythropoietin that also is found in non-hematological cells, such as the brain, and can exert significant endogenous protection in neurons during periods of cell injury.

The examples presented here of the body's ability to offer endogenous protection represent just a limited number, but more importantly raise the question of the cellular pathways that control endogenous protection and how they can be targeted for future treatment strategies in a host of disorders. In this issue of *Oxidative Medicine and Cellular Longevity*, we present a series of papers that offer new thoughts and directions to harness the power of endogenous protection in the body. In the Opinion paper by Afanas'ev, the author presents a compelling discussion that describes the stimulation and regulation of endogenous genes *p66shc*, *sirtuin*, *FoxO3a* and *klotho* related to aging and cellular injury. Some of these endogenous genes, such as *sirtuin* and *FoxO3a*, have complicated roles, but have been shown during oxidative stress to be associated with improved cell survival and longevity. Kovacic and Somanathan in their Review paper describe in detail the naturally occurring agent resveratrol, a trihydroxy stilbene, which has been shown to also activate endogenous *sirtuin* gene products that can preserve cell function and also can control lifespan of some organisms. Yamagishi and Matsui focus our attention upon metabolic disease and diabetes that lead to renal dysfunction through advanced glycation end products (AGEs). Interestingly, they describe the role of pigment epithelium-derived factor, an endogenous renal glycoprotein that has cytoprotective properties during diabetic induced oxidative stress and can limit the detrimental effects of AGEs. In their extensive Review paper on calcific uremic arteriopathy, Sowers and Hayden provide us with intriguing hypotheses upon the potential mechanism that result in the development of this disorder. One discussion entails the onset of calcific uremic arteriopathy in direct response to a reactive oxygen species-cytokine-inflammation axis that can block endogenous antioxidants such as albumin. Considerations for the targeting of this pathway for clinical utility are presented by the authors. Hamzaoui and Hamzaoui in their original study bring us to the clinical realm and provide a novel examination of the production of pulmonary B cell-activating factor of the tumor necrosis factor family (BAFF) in patients with Behcet's disease, a multi-system vascular disease. The authors demonstrate that endogenous pulmonary BAFF is up-regulated in these patients and correlates with changes in interleukins, suggesting that BAFF may have a cytoprotective role, but that BAFF also may contribute to pulmonary disease in Behcet's disease. Interestingly, Bulku et al. demonstrate for us in their work that oral application of exogenous compounds, such as their preparation of phytochemicals with thiamine and niacin, provided as a dietary supplement can be effective agents to protect against oxidant stress in the body by enhancing endogenous anti-oxidant systems such as glutathione peroxidase and superoxide dismutase. This work is further extended by the subsequent study by Goffus et al. that shows sustained infusion of the soluble B-group vitamin nicotinamide can reduce cortical brain injury and improve overall recovery in an animal model of traumatic brain injury. Although the cellular pathways responsible for the protection by nicotinamide in this study require further investigation, prior work with nicotinamide suggests that this agent may prevent cortical injury through the preservation of endogenous cellular energy stores of adenosine triphosphate. Our final paper in this issue of *Oxidative Medicine and Cellular Longevity* by Chong et al. elucidates a critical role for a secreted cysteine-rich glycosylated protein involved in nervous system development, namely Wnt1. Wnt1 is shown to rely upon the endogenous protective pathways of Akt1 tied to mitochondrial membrane function to prevent apoptotic neuronal injury. However, what is particularly exciting in this study is the demonstration that endogenous Wnt1 is necessary to preserve neuronal integrity and cortical function during oxidant stress, highlighting Wnt1 as a critical avenue in the brain for the development of

Correspondence to: Kenneth Maiese; Email: kmaiese@med.wayne.edu; aa2088@wayne.edu

Submitted: 03/12/10; Accepted: 03/12/10

Previously published online: www.landesbioscience.com/journals/oximed/article/11784

future neuroprotective treatments. Although the original interpretation of the phrase “heal thyself” was intended to counsel one to attend to individual personal deficits rather than to note deficits in others, in this issue of *Oxidative Medicine and Cellular Longevity* we have intentionally broadened the definition of this phrase to provide new insight for the body’s ability under a multitude of conditions to “heal thyself” through the direct modulation of novel endogenous cellular pathways.