Editor's Corner

Choices and outcomes

Extending basic biology to clinical care

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Both early membrane changes and immune cell activation that can eventually lead to nuclear DNA degradation occur during oxidative stress. This release of reactive oxygen species can contribute significantly to a wide range of disorders throughout the body. In many scenarios, the inciting event may be the activation of only one system in the body, such as the immune system. For example, one can consider the role of microglia in the brain. One function of microglia is to remove injured neurons and vascular cells in the brain. The role of microglia in the brain also becomes broader to form a barrier for the removal of foreign cells, such as infectious microorganisms, from the brain's parenchyma to allow for subsequent tissue repair. However as microglia function to quarantine cells for removal, they also can rely upon the generation of reactive oxygen species and the release of cytokines that may lead to the demise of previously unaffected "by-stander" cells. Given the complexity of even a single cellular population, it becomes critical for the development of new therapeutic strategies to focus upon novel studies directed to merge the understanding of cellular biology with the data acquired through prospective clinical trials.

In this issue of *Oxidative Medicine and Cellular Longevity*, we provide for our readers a number of new insights that blend unique cellular pathways with the prediction and possibilities for successful clinical care in disorders impacted by oxidative stress. Maiese et al. bring into focus the consideration of strategies that control the modulation of a host of cellular pathways including cellular proliferation, metabolism, inflammation and longevity during oxidative stress through a novel family of transcription factors. The mammalian forkhead transcription factors of the O class (FoxOs) offer exciting prospects for multiple disorders and are intimately associated with several vital signal transduction pathways, such as protein kinase B and Wingless, as well as growth factors, such as erythropoietin and insulin growth factor.

Yet, caution must be exercised with these transcription factors since FoxOs not only can promote stem cell development, cardiovascular function and cellular longevity as well as control cancer progression, but they also may lead to unwanted apoptotic cell injury and metabolic complications. Furthermore, as we learn that particular pathways may control multiple cellular functions, Junior et al. also demonstrate that different tissues and regions of the body may be more susceptible to oxidative stress. For example, the induction of protective pathways against reactive oxygen species in specific tissues may not always correlate with regions that are most at risk. These authors show that detrimental lipid peroxidation can increase in the striatum and cortex during seizures and oxidative stress, but protective pathways associated with superoxide dismutase may only increase in the cortex of the brain and exclude other vulnerable regions that involve the striatum. In any event, it appears clear that cellular antioxidant defenses appear to be important to prevent clinical disease as suggested by the work of Gomes et al. Their work implicates that the increased expression of renal superoxide dismutase and catalase during nicotinamide adenine dinucleotide phosphate oxidase elevations with aging may actually prevent hypertension and impairment of cardiac function. Interestingly, in other studies that examine aging with cardio-protective regimens against oxidative stress, Vessey et al. show that post-conditioning with ischemic/reperfusion injury was less affected by the aging process than pre-conditioning although both temporal treatments responded well with sphingosine 1-phosphate treatment. The work of these authors may suggest that additional cellular pathways during the aging process come into play that can affect cellular survival during oxidative stress in tissues such as those of the cardiovascular system. Furthermore, other agents such as manganese also may be essential to function as antioxidants during events that involve tissue cryopreservation to provide new directions for fertility treatments as shown by the work with Cheema et al. for sperm cryopreservation. In contrast, new work by Khoobchandani et al. indicates that oxidative stress pathways are sometimes required to control unregulated cellular proliferation with cancer as demonstrated with the agent *Chenopodium album*. As we look more to clinical applications, Rael et al. illustrate that agents such as phthalate esters that are used to soften storage bags for packed red blood cells may during prolonged storage ultimately lead to oxidative stress, cytokine release and inflammation in

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patients receiving transfusions. However, it should be recognized as described with the mammalian forkhead transcription factors in this issue of *Oxidative Medicine and Cellular Longevity* that cellular pathways tied to oxidative stress also may have opposing roles. Rajapakse et al. in their Extra View article show that although O-linked β -N-acetylglucosamine has been previously suggested during hyperglycemia to lead to cardiac dysfunction, O-linked β -N-acetylglucosamine also may prevent cellular inflammation in conjunction with having pro-oxidative properties. This work, in conjunction with our other articles in this issue of *Oxidative Medicine and Cellular Longevity*, provides further insight into the basis and treatment for numerous disorders tied to oxidative stress, but also brings us closer to understanding our initial discussion in regards to the immune system and the ability of microglia to choose to either assist or assassinate cells of the brain.