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Metabolic clues

Novel directives for broad treatment strategies

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Recent reports on the analysis of body weight in adolescents in the US tell us that individuals who are obese as adolescents are significantly more prone to become obese as they reach adulthood. Although it appears that many influences, such as biological, cultural and environmental variables may be factors that promote and maintain obesity with maturation, it is clear that the development of obesity can lead to multiple disorders including the development of diabetes mellitus (DM). Similarly, a number of factors such as the early exposure to dietary proteins in children also may increase the onset of DM later in life as demonstrated with recent double-blind randomized trials. As a result, the development and progression of DM in individuals has become a significant concern around the world. DM affects more than 165 million individuals worldwide and is expected to reach over 360 million individuals within two decades. DM is a prime example of a broad-based disorder that can affect multiple cellular pathways and systems of the body to lead to complications that result in immune dysfunction, depression, hepatic dysfunction, renal disease, hematological disease, neurodegenerative disorders and cardiovascular disease.

In this issue of *Oxidative Medicine and Cellular Longevity*, our initial two papers present novel analyses of pathways of DM and complications of the disease. However, given that DM is influenced by multiple exogenous and endogenous variables, we also offer a unique perspective into pathways that may be relevant to DM but are specifically targeted to different systems throughout the body. In the review paper by Haden et al., the authors open the discussion by presenting the role of pericytes in the metabolic syndrome and DM. They present strong evidence to advocate strategies that maintain this microvascular mural cell since pericytes can influence many disease processes, especially in the pancreas and skeletal muscle. In their clinical study with administration of an agent that lowers circulating cholesterol levels, Nakamura et al. investigated the role of advanced glycation end products (AGEs) traditionally present during DM in a population of non-diabetic chronic kidney disease patients with dyslipidemia. Their work reveals that with the correction of dyslipidemia, proteinuria during chronic kidney disease is reduced through pathways that are tied to the reduction in AGEs. The work illustrates that control of elevated lipid levels may confer a host of benefits for renal and cardiovascular systems given the potential protection provided against oxidative injury and the detrimental DM pathways that involve AGEs. Our next paper further extends our understanding of agents traditionally linked to the control of dyslipidemia to show that these agents also can impart protection against oxidative stress and drug toxicity. Yosef Asiri demonstrates that the cholesterol-lowering agent probucol can block the cardiotoxic effects of cyclophosphamide by improving cellular metabolic parameters and protecting the regulation of anti-oxidant pathways. However, it should be recognized that the identification of unique cellular toxic pathways is just as critical to the development of new treatment strategies as is the elucidation of alternate uses for existing agents, such as the previously described lipid-lowering drugs. In his article examining the alteration in cellular protein expression following smoke extract exposure in lung cancer cell lines and bronchiolar epithelial cells, Edward Ratovitski defines for us that loss of pathways involving LKB1 occurs in conjunction with the activation of inflammatory pathways such as COX-2/PTGS-2, potentially defining new targets and biomarkers to avert disease progression during cancer cell progression and exposure to exogenous toxins. Interestingly, oxidant pathways not only may lead to cell injury, but also may affect biological systems tied to depression and central nervous temperature regulation. Reus et al. show that treatments with antidepressant agents can reduce lipid and protein oxidation in areas of the prefrontal cortex and the hippocampus while Tang and Kiyatkin illustrate for the first time that in models with the exogenous pyrogen lipopolysacharide application elevations in brain temperature can be the result of both peripheral heat production as well as internal brain production. Each of these studies highlight for us that internal central nervous system pathways also can provide critical elements for the modulation of systemic disease presentations. In regards to systemic disease associated with the cardiovascular system, Bekki et al. tackle a common clinical problem in relation to poorly controlled hypertension. They identify antagonism of the angiotensin II receptor with specific combination therapy that proves to be most effective in controlling systolic and diastolic blood pressure. On a more cellular level for our final paper in this issue of *Oxidative Medicine and Cellular Longevity*, Lawton et al. describe a complex relationship between aspartyl-asparaginyl β-hydroxylase (AAH) and hypoxia inducible factor-1 (HIF-1) that can control neuronal cell migration. Interestingly, the work in this paper brings our readers "back to their roots" with our initial focus on DM and the multiple cellular pathways altered by DM. AAH and HIF-1 maintain a cross-talk relationship that appears to be susceptible to fluctuations in oxidative stress and signaling by insulin and insulin growth factor, echoing our work in this issue that gaining knowledge of multiple pathways throughout the body can offer novel therapeutic avenues not only for metabolic disorders such as DM, but also for seemingly unrelated disorders such as neurodegeneration and cancer.

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