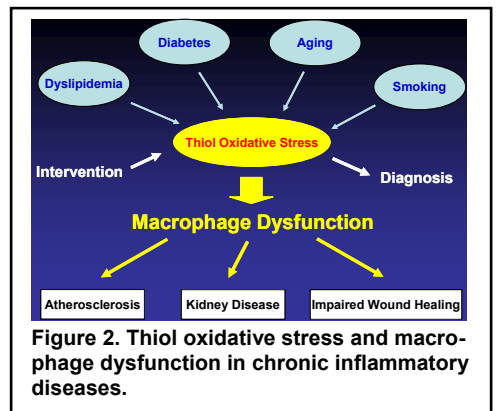
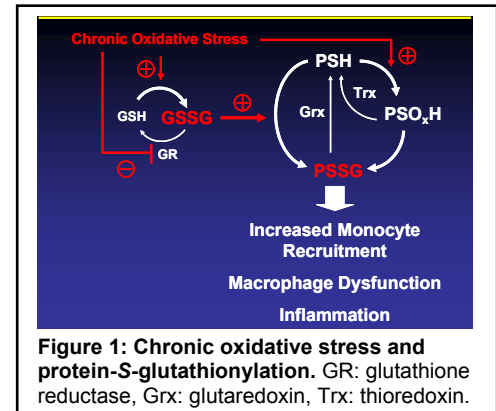


Role of Thiol Oxidative Stress in Macrophage Dysfunction Associated with Chronic Inflammatory Diseases

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Chronic inflammatory diseases are associated with monocyte and macrophage dysfunction. Our laboratory studies novel molecular mechanisms involved in monocyte/macrophage dysfunction and their role in dysregulated inflammatory processes, including atherosclerosis and impaired wound healing associated with diabetes. We found that dysfunctional macrophages not only show increased levels of ROS formation, but they also accumulate mixed disulfides (PSSG) between protein thiols (PSH) and glutathione (GSH), a process referred to as protein S-glutathionylation (Fig. 1). We could show that several features associated with monocyte/macrophage dysfunction, including dysregulated cytokine release and enhanced chemotaxis are mimicked by healthy cells that were exposed to thiol oxidants that promote protein-S-glutathionylation. Our preliminary evidence supports the hypothesis that only specific proteins are targeted for S-glutathionylation, and depending on the oxidative insult, selected signaling pathways are attenuated. Our data suggest that enhanced protein-S-glutathionylation is a common feature in monocytes and macrophages dysfunction, but that different environments may promote different S-glutathionylation patterns. The goal of our research is aimed at understanding the mechanisms leading to enhanced protein-S-glutathionylation and at identifying proteins targeted for S-glutathionylation. To this end, we are developing new redox proteomics approaches. We also generated novel transgenic mice that overexpress either glutaredoxin 1 or 2 in a macrophage-restricted manner. Glutaredoxins (thiol transferases) are small thiol-disulfide oxidoreductases that catalyze the reduction of protein disulfides and more importantly, the reduction of mixed disulfides between GSH and protein thiols. We therefore expect that monocytes and macrophages from these transgenic animals are more resistant to chronic (thiol) oxidative stress and cell dysfunction induced by a variety of environments (Fig.2).



We currently focus on three projects: a) glutaredoxins and protein-S-glutathionylation in macrophage injury and the development and progression of atherosclerotic lesions, b) the role of protein-S-glutathionylation in diabetes-induced macrophage dysfunction and impaired wound healing, and c) Nox4: a novel NAD(P)H oxidase in macrophage differentiation and function. Furthermore, we are interested in phytonutrients with anti-inflammatory properties that activate the cellular thiol antioxidant system and thus may protect monocytes against thiol oxidative stress and cell dysfunction. To this end, we are collaborating with Dr. Paolo Fanti to study the mechanisms underlying the anti-inflammatory effects of isoflavons and sylibin in hemodialysis patients, with an emphasis on the effect of these compounds on monocyte and macrophage functionalities in these patients. Together with Dr. Thomas Slaga and his colleagues, we are examining the effects of resveratrol and ursolic acid on accelerated atherosclerosis and renal injury in a new mouse model of diabetic complications.