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Abstract

The Macrophage Thiol Redox State. Its Role in Monocyte Recruitment, Atherosclerosis and Other Chronic Inflammatory Diseases.

A hallmark of chronic inflammatory diseases, including atherosclerosis, diabetic nephropathy and impaired wound healing, is the enhanced recruitment and prolonged persistence of monocyte-derived macrophages at sites of tissue injury. Metabolic disorders such as dyslipidemia and diabetes appear to be associated with monocyte dysfunction. The molecular mechanisms underlying monocyte dysfunction *in vivo* are unclear, but our recent studies in a new murine model of diabetic complications show that the glutathione redox state of macrophages is significantly impaired. Importantly, these metabolically-stressed mice showed increased monocyte chemotaxis *in vivo*, significantly increased vascular and renal macrophage recruitment, accelerated atherosclerotic lesion formation and kidney injury. Inducing metabolic stress in THP-1 monocytes *in vitro* also promotes protein-S-glutathionylation, a measure of thiol oxidative stress, and dramatically enhances monocyte recruitment in response to chemotactic stimuli. Overexpression of cytosolic glutaredoxin 1 (Grx1) or mitochondrial Grx2 protected cells from these aberrant responses, further implicating protein-S-glutathionylation in metabolic stress-induced monocyte dysfunction. Based on these observations and the emerging evidence implicating protein-S-glutathionylation in the regulation of major cell signaling pathways, we proposed that thiol oxidative stress induced by metabolic disorders promotes a state of chronic hyper-protein-S-glutathionylation, resulting in the dysregulation of monocyte responses to extracellular signals.