New Approach to Prevent Monocyte Dysfunction Associated with Metabolic Diseases

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Atherosclerosis, which is the most common cause of cardiovascular disease (CVD), is characterized by the buildup of cholesterol and other fatty substances within arterial walls, a process known as plaque formation. Two key features of atherosclerosis are the invasion of monocyte-derived macrophages into plaques as well as the conversion of these macrophages into “foam cells”. The laboratory in which this study was done has previously shown that metabolic stress caused by a high-fat diet enhances monocyte infiltration into atherosclerotic plaques by making blood monocytes hyper-chemotactic, a dysfunction that this lab showed was linked to increased oxidative stress and protein S-glutathionylation in monocytes. Protein S-glutathionylation is a reversible process by which the tripeptide glutathione is conjugated to a target protein in response to oxidative stress – this process is reversed by glutaredoxin enzymes such as Glutaredoxin 1 (Glrx1). This research project focused on identifying histone deacetylases (HDACs) that alter the expression of Glrx1, with the goal of increasing glutaredoxin expression to prevent monocyte dysfunction that leads to CVD. Using THP1 monocytes as a model, the impact of different classes of HDAC inhibitors (HDACi) on Glrx1 expression at both the transcription (mRNA) and translational (protein) levels was examined. It was concluded that the two HDACi we examined, Scriptaid and MS-275, both caused an upregulation of Glrx1 expression. These findings could have implications for drug-based interventions targeting HDAC(s) for monocyte dysfunction that contributes to atherosclerosis.