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Cancer Biology

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**Title:** Inhibition of Myeloid HDAC2 Upregulates Glutaredoxin 1 Expression Improves Protein Thiol Redox State and Protects against High-Calorie Diet-Induced Monocyte Dysfunction and Atherosclerosis.

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**Background and Aims:** The thiol transferase glutaredoxin 1 controls redox signaling and cellular functions by regulating the S-glutathionylation status of critical protein thiols. Here we tested the hypothesis that by derepressing the expression of glutaredoxin 1, inhibition of histone deacetylase 2 prevents nutrient stress-induced protein S-glutathionylation and monocyte dysfunction and protects against atherosclerosis.

**Methods:** Using both pharmacological inhibitor and shRNA-mediated knockdown of histone deacetylase 2, we determine the role of this deacetylase on glutaredoxin 1 expression and nutrient stress-induced inactivation of mitogen-activated protein kinase phosphatase 1 activity and monocyte and macrophage dysfunction. To assess whether histone deacetylase 2 inhibition in myeloid cells protects against atherosclerosis, we fed eight-week-old female and male HDAC2-/-MyeloidLDLR-/- mice and age and sex-matched LysMcretg/wtLDLR-/- control mice a high-calorie diet for 12 weeks and assessed monocyte function and atherosclerotic lesion size.

**Results:** Myeloid histone deacetylase 2 deficiency in high-calorie diet-fed LDL-R-/- mice reduced atherosclerosis in males by 39% without affecting plasma lipid and lipoprotein profiles or blood glucose levels but had no effect on atherogenesis in female mice. Macrophage content in plaques of male mice was reduced by 31%. Histone deacetylase 2-deficient blood monocytes from male mice showed increased acetylation on histone 3, and increased Grx1 expression, and was associated with increased MKP-1 activity and reduced recruitment of monocyte-derived macrophages, whereas in females, myeloid HDAC2 deficiency had no effect on Grx1 expression, did not prevent nutrient stress-induced loss of MKP-1 activity in monocytes and was not atheroprotective.

**Conclusions:** Specific histone deacetylase 2 inhibitors may represent a potential novel therapeutic strategy for the prevention and treatment of atherosclerosis, but any benefits may be sexually dimorphic.

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