Nitric oxide (NO), the endogenously produced free radical signaling molecule, is generally thought to function via its interactions with heme-containing proteins, such as soluble guanylyl cyclase (sGC), or by the formation of protein adducts containing nitrogen oxide functional groups (i.e. S-nitrosothiols, 3-nitrotyrosine, and dinitrosyliron complexes). These types of interactions result in a multitude of down-stream effects that regulate various functions in physiology and disease. Of the numerous purported NO signaling mechanisms, epigenetic regulation has gained considerable interest in recent years. Our experimental evidence has established that NO is an endogenous epigenetic regulator of gene expression and cell phenotype. We found that cellular exposure to NO modulates the activities of specific epigenetic proteins to regulate gene expression in tumors. These NO-regulated proteins control histone posttranslational modifications (PTM), DNA methylation, and RNA methylation, all of which can significantly affect transcription and/or translation. Specifically our research determined that NO exposure links modulation of histone PTMs to gene expression changes that promote oncogenesis. Recent studies demonstrated that NO could also significantly alter nucleic acid methylation which controlled the expression of tumor-permissive genes. Additionally we found that NO can increase chromatin and gene expression heterogeneity, which provide further insight into how NO mediates phenotypic plasticity in tumor cells via epigenetic modulation of chromatin dynamics.