Aberrant epigenetic gene regulation causes inappropriate gene expression, loss of cell identity, and genomic instability, and is associated with diseases such as cancer. I will present the discovery of a novel autoregulatory mechanism in a conserved enzyme that mediates epigenetic gene silencing. In its basal state, the enzyme adopts an autoinhibited conformation in which its substrate binding pocket is blocked. The enzyme acts on itself to promote a conformational switch that enhances the activity of the protein. Autoregulation locally restricts the enzyme’s activity, which prevents initiation of random gene silencing and epigenetic instability. Conservation of key residues in both closely related and more distant homologues suggest that the mechanism described here is broadly conserved.