Chemical & Physical Sciences
UNIVERSITY OF TORONTO
MISSISSAUGA

Colloquium Seminar Series
Wednesday, April 7, 2021
3:10pm via Zoom
https://utoronto.zoom.us/j/82818772109

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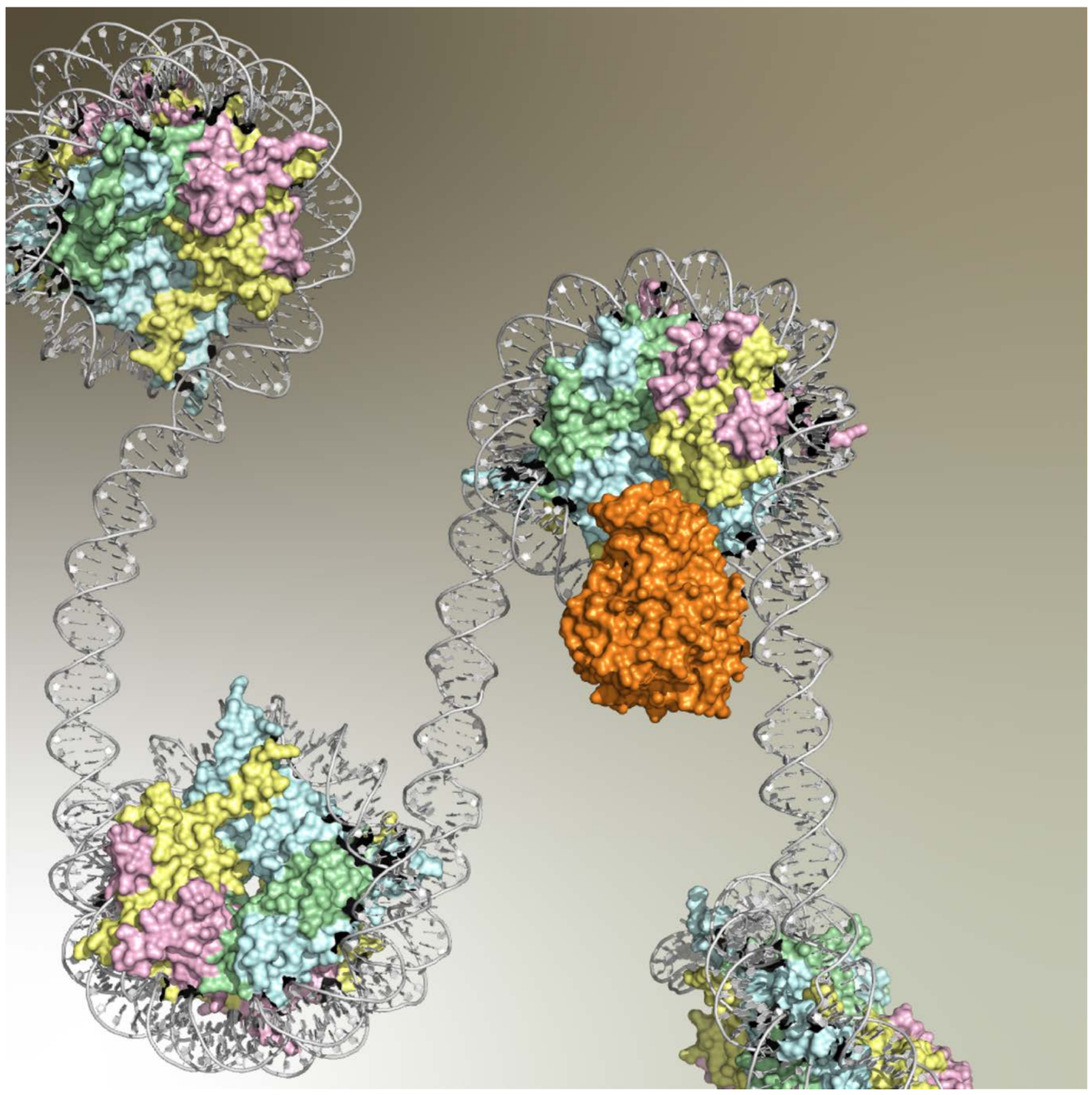
## Keeping silent takes self-control: Maintenance of epigenetic stability through intrinsic enzyme autoregulation.



Almost every cell in the human body contains the same set of genetic instructions or DNA. However, that DNA sequence gives rise to unique characteristics in different cell types. Histone and non-histone proteins package DNA forming a complex called chromatin, which help to establish cell type-specific gene expression programs by regulating access to genes. When a cell divides, its DNA is replicated and histone and non-histone proteins are distributed between the two new DNA molecules. Both daughter cells inherit identical genetic information and enough additional information, called epigenetic information, stored with the histone and non-histone proteins to reproduce the parental chromatin landscape, gene expression program, and cellular characteristics.

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.