Self-perpetuating structural states in biology, disease, and genetics

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Over the past half-century, the central dogma, in which DNA makes RNA makes protein, has dominated thinking in biology, with continuing refinements in understanding of DNA inheritance, gene expression, and macromolecular interactions. However, we have also witnessed the elucidation of epigenetic phenomena that violate conventional notions of inheritance. Protein-only inheritance involves the transmission of phenotypes by self-perpetuating changes in protein conformation. Proteins that constitute chromatin can also transmit heritable information, for example, via posttranslational modifications of histones.

Both the transmission of phenotypes via the formation of protein conformations and the inheritance of chromatin states involve self-perpetuating assemblies of proteins, and there is evidence for some common structural features and conceptual frameworks between them. To foster interactions between researchers in these two fields, the National Academy of Sciences convened an Arthur M. Sackler Colloquium entitled "Self-Perpetuating Structural States in Biology, Disease, and Genetics" in Washington, DC, on March 22–24, 2002. Participants described new phenomenology and provided insights into fundamental mechanisms of protein and chromatin inheritance. Perhaps most surprising to attendees was emerging evidence that these unconventional modes of inheritance may be common.

First described in studies of scrapie and other transmissible encephalopathies in mammals, prions were later shown to cause some classical phenotypes in yeast. In each case, an alternative protein conformation leads to formation of structures resembling amyloid fibers seen in human disease. How these are seeded has been elucidated by *in vitro* studies, leading to a satisfying picture of prion-like protein propagation. Other cases of prion inheritance have been discovered in genetic screens, which suggests that we are seeing only the tip of the iceberg. Indeed, it now appears that amyloid fiber formation is the default state for misfolded proteins, and fibrillar aggregates found in amyloidoses result from defects in the cellular machinery that prevents protein misfolding.

Excitement also pervades the chromatin field, with new insights into how nucleosomes specify and maintain distinct chromatin states. Remarkably, a single modification of a histone tail residue underlies the distinction between euchromatin and heterochromatin, and even maintenance of DNA methylation can depend on histone tail modification. From insights such as these, we have begun to realize that the relationship between chromatin conformation and gene expression might have a simple basis. Genetic and biochemical approaches have begun to elucidate how histone-modifying enzymes and nonhistone structural proteins regulate chromatin inheritance. Although these alternate mechanisms of inheritance have shaken our blind faith in the central dogma, they whet our appetite for further revolutionary insights.

This paper serves as an introduction to the following papers, which result from the Arthur M. Sackler Colloquium of the National Academy of Sciences, "Self-Perpetuating Structural States in Biology, Disease, and Genetics," held March 22–24, 2002, at the National Academy of Sciences in Washington, DC.

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