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Epigenetics: Unraveling Molecular Mechanisms and Next Generation Epidrug Design

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Perspective

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ABOUT THE STUDY

Any factor that modifies gene expression without altering the genotype or fundamental DNA sequence is referred to as epigenetic. Histone modifications that alter chromatin structure and the availability of genes for transcription, changes in DNA methylation that typically silence genes by blocking transcription factor binding sites, and the expression of microRNA antisense transcripts that target and mark mRNA transcripts for apoptosis are all examples of typical epigenetic signatures. When patterns of genetic expression are passed down to future generations through epigenetic inheritance, the core DNA sequence is not altered.

The study of heritable changes in gene expression known as epigenetics excludes or rarely involves changes in the sequence of genomic DNA. In contemporary biology, the term "epigenetics" originally related to developmental processes but has now come to refer to a relationship with gene activity, whereas the term "epigenetic inheritance" refers to the modification of gene expression without changing the DNA sequence. Over 60 years ago, a succession of lone observations in three unrelated fields of biology gave rise to the field of epigenetics. With the development of molecular biology, it gained speed, and during the last 10 to 15 years, it has evolved as a stand-alone field that is complementary to genetics.

In the last two decades, epigenetic effectors have increasingly been shown to be major regulators of nuclear processes, with direct implications for cell homeostasis, response to external stimuli, development, and onset and progression of many diseases. As a consequence, both fundamental research in epigenetics and the development of epigenetic drugs (epidrugs) for therapy have become major fields of investigation.

Initial studies focused on epigenetic enzymes involved in the deposition and removal of epigenetic marks and on the reader domains responsible for the specific recognition of these marks. Yet, the discovery that other epigenetic effectors such as histone variants, histone chaperones, and ATP-dependent chromatin remodelers are also implicated in diseases further broadens the number of targets for epidrug design. A few epidrugs are already approved for the treatment of diseases, notably cancer. Their clinical use is often accompanied by serious side effects due to the fact that many epigenetic effectors belong to families whose members are often functionally different but structurally similar. This makes selective inhibition a major issue for the design of next-generation epi-drugs. In this regard, structural data is crucial for pinpointing the molecular mechanisms underlying epigenetic processes and facilitating the development of next generation epidrugs.

Another important reason for the reduced usage of epidrugs is the strong interplay between epigenetic effectors. Notably, many epigenetic effectors act within large macromolecular complexes that represent the bona fide functional epigenetic units and that bear different epigenetic activities. First, these complexes are physically and functionally linking epigenetic activities. Thus, modulating one activity with small molecules is likely to affect the other activities. Second, regulatory subunits can change partner/substrate recognition, enzymatic activity/kinetics, and inhibitor binding. Here again, deciphering the structures of these large molecular assemblies, or at least those of their active sub-complexes, is of paramount importance for understanding epigenetic mechanisms and for aiding epidrug design.

A wealth of structural data has already been obtained on epigenetic effectors and their interactions with inhibitors, substrates, and protein partners, unraveling the diversity and complexity of these interactions. The huge amount of published structural data prevents an exhaustive description of all these results, we have chosen to focus primarily on epigenetic macromolecular complexes from the various classes of epigenetic effectors whose structures have enlarged our understanding of epigenetic mechanisms and pave the way for designing next generation selective epidrugs. In particular, macromolecular interactions and structural rearrangement mechanisms are discussed, revealing strategies for controlling the activity of epigenetic effectors.