



Binary Switches in Gene Expression: The Histone Code

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Technology Summary

The human body contains multiple organs and diverse cell types. Although every gene in the human genome exists within every cell, only a small percentage of genes are activated in any given cell type. These different gene expression profiles are formulated during early development in a multicellular organism, when cell division, cell differentiation, tissue and organ formation rapidly occur. Moreover, this gene expression potential can be “memorized” and inherited after mitosis and even meiosis. To regulate this genetic information, nature has evolved a sophisticated system that controls access to specific genes resulting in “epigenetic” information, i.e. a form of inherited states of gene regulation that lies outside of the DNA itself. This system relies on packaging DNA into a DNA-histone complex called chromatin, which is the physiological substrate of all cellular processes involving the DNA. The dynamic change of the three-dimensional architecture of chromatin makes certain genes more readily accessible to transcription factors and other machineries that must engage the genetic template.

The central building blocks of the chromatin polymer are a family of proteins named histones. Dynamic processes that covalently modify histones play critical roles in regulating gene expression. Misregulation of the “on” and “off” dynamics of histone modifications can lead to diseases such as cancer. Histone acetylation and methylation prevent DNA from coiling tightly, allowing associated genes to be expressed. The opposite processes, deacetylation and demethylation, allow the DNA to coil tightly thereby preventing gene expression.

In sum, chromatin is the physiological template of our genome. As such, the epigenetic information carried by the chromatin polymer impacts on most of the chromatin-templated processes with far-reaching consequences for cell fate decisions and for normal and pathological development. Our scientists have proposed that there is an epigenetic indexing system for our genome, a “histone or epigenetic code,” that works as a fundamental regulatory mechanism in addition to the DNA and the genetic information itself. Distinct covalent histone modifications, acting alone, sequentially or in combination, form a “histone code” that is then read by effector proteins to bring about distinct downstream events. They are currently focusing on identifying what “writes” and what “reads” the histone code.

Area of Application

- Modulation of a chromatin-binding protein or protein complex as a way to treat disease.

Stage of Development

- Discovery

Lead Inventor

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Patent Information

- U.S. Patent 8,404, 458 (issued March 26, 2013)

References

- Fischle, *et al.* 2003. *Nature*, 425:475-479.