

Epigenomic Regulation of Mammalian Development and Differentiation

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Abstract

In an effort to catalog all epigenetic marks in mammalian cells, the NIH recently launched the Epigenome Roadmap. This initiative supports the production of reference epigenome maps in a variety of primary human cells or cell lines representative of human diseases. A major challenge in epigenetic research not covered by the Roadmap however is the elucidation of how individual histone modifications contribute to the establishment and maintenance of other epigenetic marks. Addressing this question in mammalian cells has been particularly thorny because genetic deletion of histone- or DNA-modifying enzymes nearly invariably results in embryonic lethality. Another important but unsolved question relates to how individual histone modifications regulate cell differentiation, from stem cells to fully differentiated states. The aims described below will investigate these two questions in several cell lineages including human and mouse B, T lymphocytes and NK cells, in human and mouse skeletal muscle, and retinal pigment epithelial cells. In addition to regulating basic cellular processes, such as proliferation and differentiation, dysregulation of the molecules we propose to investigate has been documented in cancer, degenerative, immunological and metabolic diseases and are thus of significance to public health.