

Connecting chromatin structure, DNA methylation, and immunologic patterns

The type of helper T lymphocyte response that predominates against antigen can determine the outcomes of infectious, inflammatory, and autoimmune diseases. Distinct helper T cell subsets with unique patterns of gene expression are thought to arise from a common progenitor. In the precursor cell, signature cytokine genes appear to exist in a restrictive structure, which is determined by methylation of cytosine bases and higher-order structure of chromatin. The restrictive gene structures appear to be plastic, giving way to a more active structure in some daughter cells. Once induced, these active structures appear to be heritable over subsequent divisions. In contrast, loci encoding key transcriptional regulators, which are active in precursor cells, become heritably silenced during terminal differentiation. Strikingly, both the de-repression of silent loci and the silencing of active loci appear to be linked to the process of DNA replication. This presentation will outline the approaches taken by my laboratory to understand the way in which patterns of gene expression are altered and inherited during the cell division of helper T lymphocytes. We propose that the future study of this dynamic process can serve as a robust model system to investigate how the structure and duplication of chromosomes can inform the temporal and spatial organization of development.

References

- Mullen, A. C., High, F. A., Hutchins, A. S., Lee, H. W., Villarino, A. V., Livingston, D. M., Kung, A. L., Cereb, N., Yao, T. P., Yang, S. Y., and Reiner, S. L. (2001). Role of T-bet in commitment of T_H1 cells before IL-12-dependent selection. *Science* 292, 1907-1910.
- Mullen, A. C., Hutchins, A. S., Villarino, A. V., Lee, H. W., High, F. A., Cereb, N., Yang, S. Y., Hua, X., and Reiner, S. L. (2001). Cell cycle controlling the silencing and functioning of mammalian activators. *Current Biology* 11, 1695-1699.
- Mullen, A. C., Hutchins, A. S., High, F. A., Lee, H. W., Sykes, K. J., Chodosh, L. A., and Reiner, S. L. (2002). Hlx is induced by and genetically interacts with T-bet to promote heritable T_H1 gene induction. *Nature Immunology* 3, 652-658.
- Hutchins, A. S., Mullen, A. C., Lee, H. W., Sykes, K. J., High, F. A., Hendrich, B. D., Bird, A. P., and Reiner, S. L. (2002). Gene silencing quantitatively controls the function of a developmental trans-activator. *Molecular Cell* 10, 81-91.