Looking Farther Afield

Action at a Distance

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Ways in which cells regulate gene expression are still being discussed. The picture of all regulatory regions, strung out, like beads on a string, upstream from and in close proximity to the transcribed region of DNA, has given place to a much more dynamic picture whereby highly structured protein complexes, called chromatin, activate (euchromatin) or repress (heterochromatin) expression in a setting of a much more extensive transcriptional machine. Further, this more complex environment (with regulatory regions upstream and downstream of the start site, as well as near and far) provides a model that has proteins binding to a specific site then scanning across looped-out DNA, thus allowing the juxtaposition of distant regulatory regions with their appropriate gene.

Now, it is clear that there is further complexity: cross-talk and close physical association between regions on *different* chromosomes. Spilianakis et al. (1) studied helper T cells, which exist in a naïve state or in two specific differentiated states. Helper T cells fine tune the function of the immune system: following antigen stimulation, naive T_H cells differentiate into T_H1 cells; T_H1 cells produce, for example, IFN-γ; T_H2 cells produce a different set of cytokines, including interleukins 4, 5, and 13.

With differentiation of cellular functions in immune cells, changes in transcription are coupled with changes in localization of chromosomes within the nucleus. Genes that are silent become localized within the heterochromatin. Specific genetic loci are repositioned in such a way as to silence or permit transcription.

Spilianakis et al. studied the way in which the genes *Ifng* (chromosome 10) and *Il4* and *Il5* (chromosome 11) are controlled. Although on separate chromosomes, the two regulatory regions are in close proximity in the naïve helper T cells but move away from each other after antigenic stimulation that induces maturation to T_H1 or T_H2. Following antigen exposure that will result in a T_H1 cell, for instance, the gene for IFN-γ is up-regulated and the T_H2 genes (say *Il4* and *1l5*) are switched off. This appears to be accomplished by having the relevant region of chromosome 11 move to a heterochromatin-repressed region of the nucleus. That the interaction between chromosomes is indeed important is underlined by the data showing that deleting a regulatory element for the T_H2 regulatory control region (chromosome 11) disrupts the expression of *Ifng* (chromosome 10).

Is this interchromosomal cross-talk a feature only of genes in the immune system or is it a more widespread (even common) phenomenon? If this phenomenon is a general one, can we any longer be sure about the ways in which allelic variants might influence each other across the apparent barrier of being on separate chromosomes? If that is a relevant question, how might meiotic recombination further perturb this picture? Which finally leads to the question, do we have to rethink assumptions underlying genetic linkage studies?—John D. Potter

Reference

1. Spilianakis CG, Lalioti MD, Town T, Lee GR, Flafovell RA. Interchromosomal associations between alternatively expressed loci. Nature 2005;435:637–45.

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doi:10.1158/1055-9965.EPI-06-0105