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NEWS AND COMMENTARIES

Gene Expression

Growing up together may help genes go their separate ways

Vania Parelho and Matthias Merkenschlager

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New work just out in *Nature*[1] demonstrates that genes from different chromosomes can be found together in the nucleus and that this may facilitate their coordinated regulation.

The human genome is often represented as a one-dimensional sequence, but an entirely different perspective is required for understanding how the genome actually functions. Roughly 2 m of DNA is contained in a nucleus that is only a few microns across, and this maze is negotiated by transcription factors, chromatin proteins, machines that remodel chromatin, transcribe DNA into RNA, process RNA transcripts or replicate DNA in preparation for cell division. Far from being chaotic, these activities appear to be ordered, with particular activities like transcription or replication taking place at specific locations within the nucleus. For example, 'transcription factories' churn out multiple different transcripts and 'replication factories' initiate DNA replication at several origins.[2] While the spatial organisation of the genome within the nucleus has been described in considerable detail,[3] not much is known about how this organisation is established and what functional significance it has.

In contrast to prokaryotes and lower eukaryotes, genes in higher eukaryotes are often controlled by multiple regulatory elements, such as promoters, enhancers and boundary elements, which can be located at considerable distances from each other and the coding region.[4,5] To explain how this works, novel techniques have been used to infer the three-dimensional organisation of several loci. The chromosome conformation capture (CCC) approach taken by these studies infers colocalisation of distinct DNA or RNA sequences from how often they are found together when cells are fixed to crosslink their nuclear components. Pioneered by Nancy Kleckner's lab in yeast,[6] the CCC approach has been applied to a spectrum of mammalian genes including the beta globin locus, immunoglobulin genes, the imprinted Igf2/H19 locus and the cytokine locus on mouse chromosome 11 (reviewed by West and Fraser[5]). Collectively, these studies suggest that looping in three-dimensional nuclear space brings *cis*-acting sequences together to regulate gene expression. The DNA sequences that initiate these interactions[7] and the DNA-binding factors that mediate them[8] are only just beginning to be defined.

An important addition to the concept that transcription factors bind to critical elements and – directly or indirectly – bridge distant regulatory elements was made last year.[9] Peter Fraser's lab showed that – in addition to interactions in *cis* – genes on different chromosomes can come together at shared sites of transcription. In their new *Nature* article,[1] Richard Flavell and colleagues have further extended these ideas. They show that, even in the absence of active transcription, cytokine genes on different chromosomes colocalise in the nucleus of naive helper T cells. The authors used both CCC (see above) and fluorescence *in situ* hybridisation (FISH) to show that the IFNg locus on mouse chromosome 10 and a cluster of Th2 cytokine genes comprising IL-4, IL-15 and IL-5 (the Th2 cytokine gene locus) on chromosome 11 physically interact *in vivo* (Figure 1). A sequence element required for three-dimensional interactions within the Th2 cytokine gene locus, called RHS-7,[7] is also critical for interchromosomal interactions with the IFNg locus.[1]

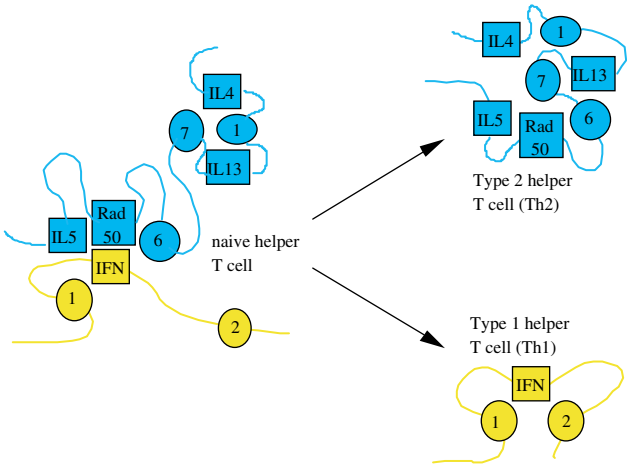

Figure 1 Interchromosomal interactions between promoters (rectangles) and other regulatory elements (ovals) of the Th2 locus on chromosome 11 (blue) and the interferon gamma locus on chromosome 10 (yellow) in naive helper T cells. Following differentiation of naive helper T cells into specialised helper cells that either use the Th2 locus or the interferon gamma locus (Th1), interchromosomal interactions between the Th2 locus and the interferon gamma locus are weakened and new intrachromosomal interactions are formed selectively in Th1 or in Th2 cells. The selected elements shown on chromosome 11 (blue) are as follows – IL5: interleukin-5; 6: hypersensitive site 6 (RHS-6); 7: RHS-7; IL13: interleukin-13; 1: conserved noncoding sequence 1 (CNS1); IL4: interleukin-4; and on chromosome 10 (yellow) – IFN: gamma interferon; 1: CNS1; 2: CNS2.

Perhaps the most interesting aspect of these studies is the finding that interchromosomal interactions are not found in just any cell type, but specifically in naive T cells. This is important because naive helper T cells have the potential to transcribe both IFNg and the Th2 cytokine gene locus upon activation. Subsequently, helper T cells differentiate into highly specialised cells with distinct functions in the immune system, which express either IFNg or the Th2 cytokine gene locus, but not both.[10] These differentated Th1 and Th2 cells no longer have the potential to coexpress both loci, and the interchromosomal interactions between IFNg and the Th2 cytokine gene locus are lost to be replaced by new intrachromosomal contacts (Figure 1). The authors point out the exciting possibility that genes may colocalise in the nucleus in readiness for their coordinated expression. In support of this idea, Flavell and colleagues demonstrate that removing the RHS-7 sequence from the Th2 cytokine gene locus compromises its interaction with the IFNg locus and – most significantly – the expression of the interaction partner, IFNg.

The new findings raise several burning questions. Those of us who work on developmentally regulated genes will want to find out how general the new findings are. Will they apply to other genes poised for coordinated expression? If so, will interchromosomal interactions change when one or the other of the interacting partners is excluded from expression during development? Will the authors' interpretation that colocalisation prepares genes for coordinated expression hold up for other interacting genes, or will interchromosomal interactions turn out to have other functions? There are suggestions that they will. For example, human cells contain several hundred ribosomal (rDNA) genes distributed over five chromosome pairs, and rDNA genes from several chromosomes merge to form a single nucleolus.[11] Inactive genes from different chromosomal addresses have also been found together, in association with polycomb proteins[12] or in the vicinity of centromeric heterochromatin.[13] The most important question concerns the mechanisms that set up and disperse these interchromosomal interactions. If we can define the molecules involved, we will be in a great position to understand more about the way in which patterns of gene expression are established and progressively modified during development■

V Parelho and M Merkenschlager are at the Lymphocyte Development Group, MRC Clinical Sciences Centre, Du Cane Road, London W12 ONN, UK.
Tel: +44 (0) 20 8383 8239;
Fax: +44 (0) 20 8383 8338;
E-mail: matthias.merkenschlager@csc.mrc.ac.uk

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Research Networks

BioSapiens: a European network for integrated genome annotation

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The BIOSAPIENS Network of Excellence exists to provide infrastructure to support laboratories across Europe in annotating genome data using both bioinformatics tools and experimental data. The annotations generated by the network will be made available in the public domain and easily accessible on the web.

The first draft of the human sequence, published in 2001, was followed by other related genomes and the detailed resequencing of the human genome. This