4-1997

Chromosomes and expression mechanisms

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Editorial overview

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Current Opinion in Genetics & Development 1997, 7:149–151

Electronic identifier: 0959-437X-007-00149

Abbreviations

ATM	ataxia telangiectasia mutated
ATR	ataxia telangiectasia and Rad 3 related
ELL	11–19 lysine-rich leukemia
FRAP	FKBP12 and rapamycin-binding protein kinase
LCRs	locus control regions
MCM	minichromosome maintenance
ORC	origin recognition complex
TAFs	TATA-box binding protein associated factors
USA	upstream stimulatory activity

As expected, the past year has seen many advances in our understanding of chromatin/chromosome structure and the regulation of gene expression. Most notable has been the increasing synthesis of observations based on biochemical approaches, genetics and structural studies. In this year's *Chromosomes and expression mechanisms* issue of *Current Opinion in Genetics & Development*, we include reviews on DNA replication and repair; the role of nucleosomes in the regulation of gene expression; transcription initiation and elongation, RNA processing, transport and translation; the organization of the genome into alternatively packaged domains; and the impact of genome organization on the function of chromosomes and on physiological processes such as aging.

The replication of the genome is perhaps the most fundamental and important biological event and this past year has witnessed major developments in our understanding of this process and how this is controlled. For example, much headway has been made in our appreciation of the origin recognition complex (ORC), which plays a crucial role in initiating semi-conservative DNA replication. Although ORC was identified originally in yeast, the recent cloning of ORC subunit homologues from a wide variety of other eukaryotes, including humans, attests to there being strong evolutionary conservation in the fundamental mechanisms of DNA replication control and opens up the way for exciting future developments. There has also been much learned about the MCM/P1 components of the replication licensing factor, which plays a crucial role in ensuring that DNA is replicated once and only once per cell cycle. Rowles and Blow (pp 152–157) review these developments and also discuss other recent advances regarding the control of DNA replication and the identification of replication origins in higher eukaryotes.

Another section of research that has continued to receive a huge amount of attention over the past year is DNA repair; some of the advances in this area are reviewed for us by Lindahl, Karran and Wood (pp 158–169). These authors pay particular attention to DNA excision repair pathways that repair endogenously-generated base lesions and DNA damage that is inflicted by ultraviolet light. Major advances include determining the structures of DNA glycosylases and their target lesions, the establishment of defined *in vitro* systems for base excision repair, and the cloning of the gene for the last of the core mammalian nucleotide excision repair factors. Other important areas covered include developments regarding the linkage of DNA repair defects to certain human genetic disorders and the creation of mouse models for these conditions. On a somewhat related subject, Hoekstra (pp 170–175) describes recent advancements regarding proteins of the DNA-PK_{cs}/ATM protein kinase family, many members of which play crucial roles in DNA repair, cell cycle control and/or DNA damage signalling. In particular, there have been significant strides forward in our understanding of DNA-PK_{cs} and its associated Ku subunits, and in determining the mechanisms by which FRAP influences cell cycle progression and protein translation. Finally, the linkage of ATM and ATR to meiotic recombination events and the possible association of the BRCA1 breast cancer susceptibility protein with this process have further extended the set of biological phenomena controlled by members of the ATM protein family and have created a great deal of excitement recently.

A major interest that has developed over the past several years is to discern how the many regulatory signals from enhancers and other *cis*-acting elements interact with the general transcription machinery to achieve the appropriate level and control of transcription initiation. There has been significant recent progress in this area that has lead to the further characterization of three apparently distinct classes of cofactor that act, sometimes in an activation domain-specific manner, to relay regulatory information to the basal transcription complex. Sauer and Tjian (pp 176–181) have reviewed for us the current information on the cofactors termed USA, mediator and TAFs, and have compared and contrasted findings in yeast, *Drosophila*, and human cell systems. The differences in these systems are proving to be as important as the similarities in providing mechanistic insights into basal and regulated transcription.

Many recent findings have contributed to our appreciation of the active role played by histones in regulated gene expression in eukaryotes. With the identification of several ATP-dependent nucleosome remodelling factors, we are beginning to discern both the common and the distinctive features of these activities. Particularly important will be work to identify the means by which such activities are targeted to specific genes. Exciting findings have continued to emerge from the work on histone acetylation, a modification critical both for the initial assembly and for the remodelling of nucleosomes. Identification of genes encoding histone acetylases and deacetylases has shown that several of these activities were already known to be involved in transcription or chromatin assembly and has provided new insights into these functions. Genetic evidence has confirmed a direct role for the histones not only in the remodelling process but also in the activity of several transcriptional regulators. Perhaps most surprising has been the observation that the linker histones are not essential—as shown in *Tetrahymena*—but do affect the regulation of some genes in a specific fashion. These studies and other recent advances are reviewed by Tsukiyama and Wu (pp 182–191) and by Hartzog and Winston (pp 192–198).

Although work in the transcription field has traditionally focused most heavily on transcriptional initiation, accumulating data suggests that transcriptional elongation and termination are also very important sites for regulatory control. One area of particular interest recently has been the process of transcriptional pausing by RNA polymerase II and how this is influenced by upstream transcriptional activators, RNA polymerase carboxy-terminal domain phosphorylation and chromatin structure. Another has been to determine the mechanism of action and biological functions of general elongation factors such as SII, P-TEFb, TFIIF, Elongin and ELL. These subjects are reviewed for us by Shilatifard, Conaway and Conaway (pp 199–204). In addition, these authors discuss exciting recent findings which have linked defects in ELL with acute myeloid leukaemia and have shown that Elongin appears to be regulated by the tumour suppressor protein VHL.

Most RNA transcripts in higher eukaryotic cells are processed before they are exported to the cytoplasm and it is now clear that these events are subject to regulation. Some of the most significant recent developments in this field have concerned pre-mRNA splicing and its control. Wang and Manley (pp 205–211) review this subject with specific emphasis on the SR family of proteins, which are required for spliceosome formation in higher eukaryotes. Notably, these proteins play a multitude of functions in the splicing process, including helping to bring the 5′ and 3′ splice sites together, recruiting snRNPs to the spliceosome, and promoting interactions between snRNPs and splice sites. The findings that SR proteins play positive and negative roles in controlling differential splicing and appear to be regulated by phosphorylation indicate that these and other regulators of splicing play crucial roles in a wide variety of important cellular processes.

Another area that has received much attention over the past year is the subject of RNA transport into and out of the nucleus. Whereas most species of RNA are transported unidirectionally, the situation for certain U snRNAs is more complex: after export, these are packaged into snRNP complexes which are then re-imported into the nucleus. Additional evidence for such complexity is provided by the existence of distinct transport pathways for different RNA species and by evidence suggesting that RNA transport is subject to regulation. Lee and Silver (pp 212–219) review developments in this field, paying particular attention to the mechanistics of RNA transport and its linkage with protein export/import pathways.

Once it has entered the cytoplasmic milieu, the next job for most mRNA species is to engage with ribosomes to direct the expression of a particular protein. Although it has been clear for some time that this process is subject to extensive regulation, the precise mechanisms by which this occurs are only now beginning to become appreciated fully. Some of the recent developments in this extensive subject are covered in two complementary articles provided by Wickens, Anderson and Jackson (pp 220–232) and by Jackson and Wickens (pp 233–241), which focus primarily on events impinging on the 3′ and 5′ ends of the mRNA respectively. In addition to covering the mechanistics of these regulatory processes, these authors discuss how ribosome function is itself regulated by environmental stimuli and draw attention to the importance of translational control and mRNA localization in developmental processes.

Given the promiscuous nature of enhancers, a major puzzle in our analysis of chromosomes has been how to maintain the regulatory integrity of the individual gene: what mechanisms enable an enhancer to affect the appropriate gene without affecting neighbouring genes? 'Insulators' with this apparent function have been identified previously in *Drosophila* and are found as components of more complex regulatory elements, the LCRs, in other organisms. Progress has been made this year in dissecting these elements, reviewed by Geyer (pp 242–248). Insulators—or 'boundary elements'—generally function only as part of a chromosome, suggesting a mechanism dependent

on chromosome structure or organization. Genetic analysis of insulators and of modifiers of insulator function holds promise for developing an understanding of how these elements actually work, something that remains a mystery.

The subdivision of the chromosome into functional domains is also of critical importance for establishing specificity in silencing, the stable inactivation initially characterized in heterochromatic regions. Recent studies have suggested many parallels between such heterochromatic silencing and the maintenance of stable inactivation of developmentally regulated loci achieved by the Polycomb system in *Drosophila*. The establishment of multiprotein complexes — with key proteins recruiting others to the specific loci to be silenced — appears to be a critical event. New data continue to support the idea that the extent and stability of the silenced domain reflect the concentration of the components, suggesting a competition between alternative chromatin states. This work has been synthesized for us by Pirrotta (pp 249–258). Again, new findings have pointed to a role for histone modification, both acetylation and ubiquitination, in establishing and/or maintaining a silenced state. In addition, new data have highlighted the importance of nuclear localization in silencing. Dramatic advances have been made over the past several years in the use of fluorescence *in situ* hybridization and three-dimensional microscopy, leading to a more detailed picture of positional order in the interphase nucleus. Progress has been made in identifying those local molecular interactions that can be used to establish a global nuclear architecture; this is reviewed by Marshall, Fung and Sedat (pp 259–263).

Major progress has been made in the past year in defining the portions of the chromosome — both DNA and protein components — required for centromere formation in several organisms and for X chromosome inactivation in mammals; these topics are reviewed by Allshire (pp 264–273) and by Lee and Jaenisch (pp 274–280), respectively. An epigenetic effect appears to operate in the formation of functional centromeres in yeast; the possible mechanistic connections between heterochromatin formation, centromere formation, and X inactivation are intriguing. Dramatic progress has been made recently in establishing a link between kinetochore function and mitotic forces; it appears that tension across kinetochores in mitosis erases a signal, a phosphoepitope, that acts to inhibit anaphase onset in mammalian cells. Progress has also been made in recognition of the proteins involved in sister chromatid cohesion and subsequent separation; here, as in regulation of other cell cycle events, one observes the importance of protein degradation in 'irreversible' signaling. New studies on mammalian X chromosome inactivation have provided a better definition of the X inactivation center, indicating that it may be contained entirely within a 450 kb fragment, and have shown the *Xist* locus to be required for — and directly involved in — *cis*-restricted silencing.

The importance of silencing has also been suggested by studies on aging in *Saccharomyces cerevisiae*, which suggest that a failure in the regulation of silencing is a key event in senescence. Regulation of telomere length and its role in senescence and cellular immortalization has been found to be more complex than was previously supposed. Various aspects of DNA metabolism are also implicated in aging; 1996 saw the isolation of the Werner's syndrome gene and its identification as a putative DNA helicase. Genetic screens for long-lived organisms, however, have implicated other controling mechanisms too; work on mechanisms of cellular senescence has been reviewed by Smeal and Guarente (pp 281–287). One can anticipate that, in years to come, an increasing part of our attention will be devoted to understanding how the decisions made at the genome level — the rate of individual gene transcription, RNA processing and transport, and the silencing of domains — are played out in terms of the developmental patterns of the organism.