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Coordination of epigenetic events

A. El-Osta

The Alfred Medical Research and Education Precinct (AMREP), Baker Medical Research Institute, Epigenetics in Human Health and Disease Laboratory, Second Floor, Commercial Road, Prahran, Victoria 3181 (Australia), Fax: +61 3 8532 1100, e-mail: assam.el-osta@baker.edu.au

Abstract. During the course of DNA damage a complex repertoire of molecular signals, chromatin determinants and specific transcription factors are set in motion for repair. In many instances, the response pathway can be characterized by profound changes in molecular remodeling and is intimately linked with DNA replication and gene transcription. Our understanding of the molecular pathways has come from scientific developments that represent many disparate disciplines, such as cancer (epi)genetics, chromatin modifications during cellular development and the emerging prominence of epigenetic events in human disease. These multidisciplinary areas reveal a functional relationship and suggest that repair and transcription must coincide in the context of chromatin. We have come to appreciate the repair process and the role of transcriptional components in a sophisticated program of epigenetic regulation, and we have learnt much since the first description of the nucleosome as a spheroid disklike unit. The coordinated and ordered response to DNA damage can specify structures that mobilize and remodel nucleosomes. Investigators will undoubtedly continue to explore the structural and functional states of DNA damage repair and continue to profile the sequence of events and scrutinize the molecular signatures that specify these changes in chromatin dynamics, genomic stability and transcriptional performance. In this special issue, authors have contributed reviews that discuss hypotheses and results regarding DNA damage repair and transcription. The topics covered range from DNA repair in a chromatin environment to the deadly double-strand break, histone modifications to ATP-dependent chromatin remodeling, gene silencing in cancer to apoptosis and regulation of chromatin dynamics by DNA methylation. The scene is set for a new view of damage detection and repair by the coordination of epigenetic states.

Key words. DNA damage; transcription; chromatin modification; epigenetic regulation.

The multi-author reviews of this issue of *Cellular and Molecular Life Sciences* are devoted to the topic of 'DNA damage repair and transcription'. The contributions have a distinctly epigenetic component and typify the recent surge of interest in epigenomics in attempts to understand fundamental processes involved with DNA repair and transcriptional competence within a chromatin environment [Karagianis and El-Osta, 2004; Wuebbles and Jones, 2004; Verger and Crossley, 2004; Bowen et al., 2004; Soejima et al., 2004; Berardi et al., 2004, *Cellular and Molecular Life Sciences* this issue]. The detection of damaged DNA is essential to ensure genomic stability and underpins the cellular defence mechanism. The dividing cell has developed complex mechanisms of repairing DNA lesions in chromatin which has been reviewed exquisitely by Almouzni et al. [1].

The first review by Karagianis and El-Osta discusses recent progress in the repair of the most severe form of DNA damage – double-strand breaks (DSBs). Characterizing the DSB repair pathway has revealed a complex mechanism dependent on chromatin modification, surveillance, mobilization and repair. The observations that DSB-induced histone modifications such as acetylation and phosphorylation firmly connect chromatin modifications with repairing damaged DNA immediately suggests that repaired sites must gain access to the nucleosome core. Wuebbles and Jones discuss the structural packaging of chromatin as the key element of the highly dynamic nucleosome unit. The typical mammalian nucleus must package 2–3 billion bases or close to 2 meters of human DNA in a highly structured manner whilst maintaining access and mobility for many of the core nuclear

functions. It is now evident that a role for specialized chromatin structures mediating transcriptional control and DNA repair are critical in these processes. For example, DSBs can activate the repair pathway even at a distance from the actual DNA lesion, further highlighting the remarkable nature of chromatin dynamics. How epigenetic changes such as perturbations in chromatin structure regulate function of the repair process is not yet clear, although recent evidence suggests that an initiating event includes activation of the ATM kinase by phosphorylation [2]. Such studies provide bona fide link between posttranslationally modified histones and activation of damage repair events. We have discovered a great deal of information about chromatin organization and assembly in almost 3 decades to extend beyond that of early interpretations of the disk-shaped nucleosome unit [3].

Transcriptional regulation events are featured by key changes in histone modification and active movement of the nucleosome by ATPase-dependent remodeling machines. Verger and Crossley elegantly assess chromatin modifiers in transcription and repair and discuss the recruitment of molecular determinants that regulate transcriptional competence and participation in damaged nucleosomes. Given that modification of histones regulates chromatin structure and function, the authors discuss the implications of active chromatin remodelin-dependent enzymes. Transcriptional regulation involves the complex interactions of several different components. The structural state of chromatin can be regulated by at least three different strategies of which we have already discussed two: covalent modification of histones and ATP-dependent movement of chromatin. The third category involves the differential association of non-histone proteins such as the methyl-CpG binding domain (MBD) proteins. The prototype of the MBD family is MeCP2, a methyl-CpG-binding protein that associates with histone deacetylase corepressor complex. In order to understand the correlation between transcriptional control and chromatin regulation, Bowen et al., consider the accumulating biochemical data that connects DNA methylation with changes in chromatin structure and transcriptional function. Epigenetic silencing of genes is closely associated with DNA methylation, and the mechanisms underlying the targeting of CpG methylation and the subsequent repression of transcription are relevant to transcriptional control, chromosomal stability and cancer development. The review by Soejima et al. discusses this connection with DNA damage repair and also elaborates how these components associate together to directly impact on transcription and replication.

The review by Beradi et al., raises a host of intriguing questions regarding the link between transcription, DNA repair and apoptosis. For example, could chromatin remodeling in the absence of a DNA damage signal activate a repair pathway? Furthermore, what molecular events are involved in differentiating a remodeled nucleosome as a consequence of DNA damage from that of transcriptional activity or DNA replication during cell division? The authors discuss the significance of ING proteins to coordinate DNA damage repair and support transcriptional control.

This series of multi-author reviews highlights some of the key discoveries that directly impact on current paradigms of detection, signaling and repair. Chromatin modification influences a myriad of nuclear events that include DNA structure and genomic integrity. The exquisite organization of chromatin and condensing of the genome by histone and non-histone proteins uncovers highly dynamic regulatory processes that impact on DNA damage repair, transcriptional fitness, genome replication and recombination events. Recent experimental evidence firmly links regulatory signals imparted by epigenetic modifications with DNA damage repair and transcription. These developments chronicle an important time in the field and provide an excellent precedent for future research.

1 Gontijo A. M., Green C. M. and Almouzni G. (2003) Repairing DNA damage in chromatin. Biochimie **85:** 1133–1147
2 Bakkenist C. J. and Kastan M. B. (2003) DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature **421:** 499–506.
3 Olins A. L. and Olins D. E. (1974) Spheroid chromatin units (v bodies). Science **183:** 330–332