Meeting report

Celebrating 40 years of biochemistry in Europe

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A report of the 29th Congress of the Federation of European Biochemical Societies (FEBS), Warsaw, Poland, 26 June-1 July 2004.

The 29th Federation of European Biochemical Societies (FEBS) Congress, held in Warsaw, Poland, was judged by the organizers as an appropriate opportunity to celebrate the 40th anniversary of the founding of the FEBS. This organization, now with a membership of about 40,000 scientists representing 36 constituent societies and 6 associated member societies, was formally launched in 1964. The meeting was, of course, quite general in its coverage of biochemistry and molecular biology, but this report focuses on the 'DNA realm' symposium, with a particular emphasis on mutagenesis and DNA repair. First, however, we draw attention to the opening of the formal scientific program with the Datta Lecture given by Kurt Wüthrich (Swiss Federal Institute of Technology, Zurich, Switzerland). Wüthrich, recipient of the Nobel Prize in Chemistry in 2002, boasts a professional career in magnetic resonance spectroscopy that has lasted more than 40 years. His lecture reviewed the history of the use of nuclear magnetic resonance (NMR) spectroscopy for understanding macromolecular structure, especially that of proteins. Wüthrich emphasized the limitations that the original one-dimensional NMR techniques placed on the size of proteins whose structure could be usefully examined, and contrasted this with the great progress in deciphering protein structure that came with the advent of two-dimensional NMR, beginning in the late 1990s. Wüthrich illustrated several notable examples of this progress, in particular the elucidation of the structure of prions and, more recently, the structures of membrane proteins reconstituted in water-soluble detergent micelles.

The burgeoning field of 'DNA repair and mutagenesis' might be more informatively designated as 'biological responses to DNA damage', given that it now firmly embraces many aspects of cellular responses to genetic insult besides DNA repair and the generation of mutations, including cell-cycle checkpoint control in the face of DNA damage, transcriptional activation of many genes, and sometimes apoptosis (Figure 1). Oxidative base damage to DNA is a prominent source of spontaneous DNA damage that has important implications for various diseases, and especially cancer. Oxidative damage featured prominently in presentations at the symposium on the general theme of biological responses to DNA damage, but cellular responses to many other types of DNA damage were also represented.

Josef Jiricny (University of Zurich, Switzerland) presented interesting new findings on DNA-damage signaling during mismatch repair of DNA. It is well established that mammalian cells defective in mismatch repair are more resistant to alkylation damage to their DNA - so-called alkylation tolerance. In normal cells it is believed that DNA containing mispaired bases (where one of them is alkylated) undergoes futile cycles of DNA degradation that are continually initiated at the mismatch, but the precise mechanism of cell death during this process has not been defined. Jiricny and his colleagues have shown that cell death occurs by arrest in the G2 or M phases of the second cell cycle after alkylation treatment. This arrest is activated by two proteins, ataxia telangiectasia mutated (ATM) and ATM and Rad3 related (ATR) proteins, as well as the Chk1 and Chk2 protein kinases, which are required for normal checkpoint control. Thus, mistmatch repair initiates a complex signaling pathway. Studies by Jiricny and colleagues also suggest that DNA-damage signaling and the process of mismatch repair can be uncoupled, hinting at

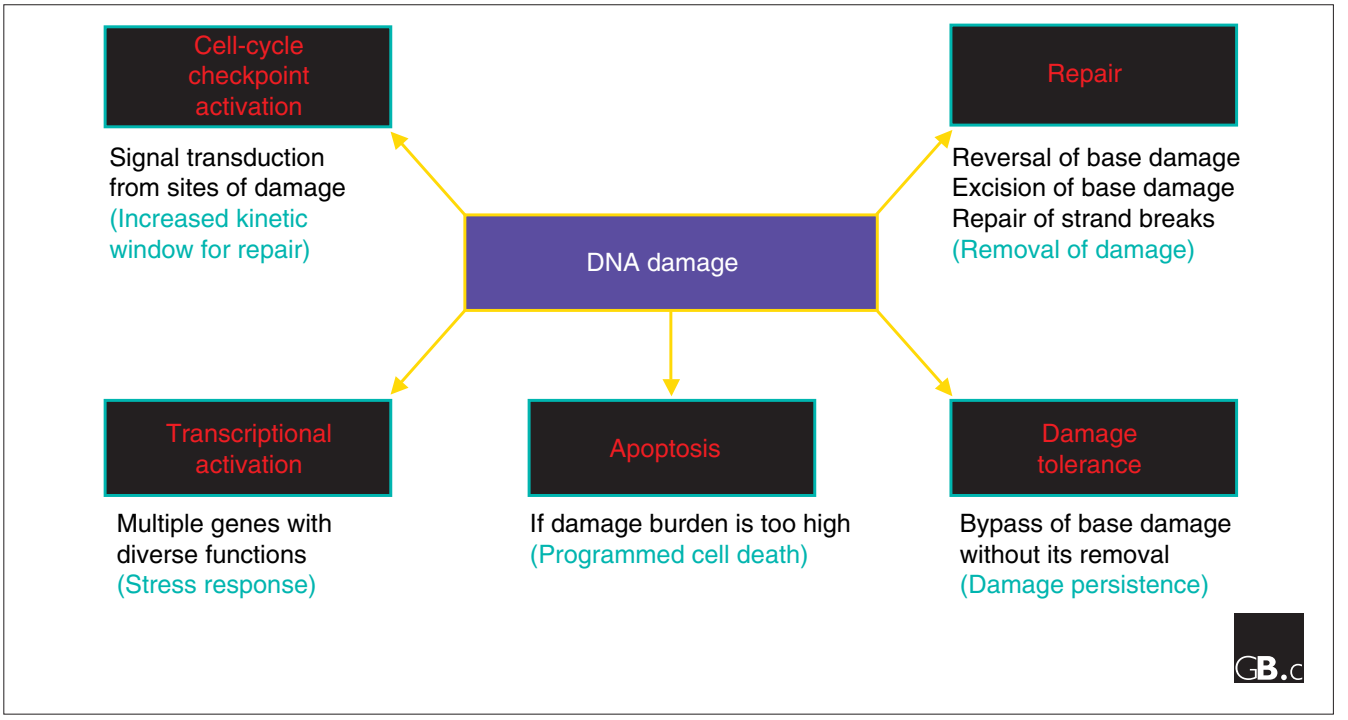

Figure 1
A summary of cellular responses to DNA damage. Responses are shown in boxes, with details of how the cell responds below the box; the outcome of the response is shown in brackets.

dual, separable functions for some proteins that are involved in mismatch repair.

Leon Mullenders (Leiden University, The Netherlands) presented a new technical nuance that may finally shed light on some of the mysteries of the process of transcription-coupled nucleotide-excision repair (TC-NER) of DNA. This process has long been known to operate preferentially on the transcribed strand of transcriptionally active genes. In addition to the usual components of the NER machinery, with the notable exception of xeroderma pigmentosum protein C (XPC), TC-NER requires specific components that include the Cockayne syndrome (CS) proteins CSA and CSB. Other proteins have also been implicated in the TC-NER process, including the XPG protein. Definitive inroads into the biochemistry of TC-NER have been limited by the failure to date to establish cell-free systems that reproduce this process specifically. Exploiting chromatin immunoprecipitation (ChIP) technology, Mullenders and his colleagues have enriched for regions of genomic DNA in which the RNA polymerase II transcription machinery is apparently arrested at a cyclobutane pyrimidine dimer (CPD). Western blot analysis of the components of these DNA fractions reveals the presence of the CPD plus RNA polymerase II, NER proteins (excluding XPC) and CS proteins. Continued detailed analyses of this type are likely to yield important new information on the proteins that are specifically required for TC-NER. Additionally, the deployment of different types of base damage may help resolve the controversy as to whether or not a transcription-coupled form of nucleotide-excision repair exists in mammalian cells.

The repair of the highly mutagenic DNA lesion 8-oxoG in the base-excision repair pathway was described by Serge Boiteux (Commissariat à l'Energie Atomique, Fontenay aux Roses, France). The repair reaction is initiated in eukaryotic cells by the DNA glycosylase OGG1. The initial recognition and 'flipping-out' of 8-oxoG and cleavage of the base-sugar bond by OGG1 constitute the rate-limiting steps in the repair pathway *in vivo*. All subsequent enzymatic steps occur rapidly and in a co-ordinated fashion, so the accumulation of DNA strand breaks and other reaction intermediates is not detected. The co-ordination of the repair functions prior to the generation of a DNA single-strand break is aided by the fact that turnover by OGG1 is slow by itself, but the reaction is greatly stimulated by the next enzyme in the pathway, the APE1 endonuclease that acts on apurinic sites. There is also a slight stimulation of OGG1 activity in human cells by the XRCC1 scaffold protein that helps to co-ordinate the different components of the latter steps of the pathway. The OGG1 and APE1 enzymes bind to the same domain of XRCC1.

The labile iron pool in cells is of critical importance for the introduction of DNA single-strand breaks after exposure to

hydrogen peroxide. This issue was discussed by Marcin Kruszewski (Institute of Nuclear Chemistry and Technology, Warsaw, Poland). He reported that the easily chelatable iron, present both as Fe^{2+} and Fe^{3+}, represents only 3-5% of the total iron in a cell and is typically present at a concentration of 5 μM in liver-cell nuclei. DNA damage induced by nitric oxide (NO) is also dependent on the labile iron pool, because the active form of NO in this context may be a dinitrosyl-iron complex. Like iron, copper promotes the Fenton reaction, leading to increased lipid peroxidation and DNA damage by formation of etheno-adducts of adenine and cytosine. Helmut Bartsch (German Cancer Research Center, Heidelberg, Germany) described Wilson's disease, in which a dysfunctional ATPase results in impaired Cu^{2+} transport in hepatocytes, leading to increased intracellular levels of the metal. Bartsch reported that in a transgenic mouse model of Wilson's disease, the animals get liver cancer within a year. An elevated steady state of the etheno-adenine DNA lesion occurs in the liver in Wilson's disease, and has also been observed by immunostaining of sections of cirrhotic liver.

Yosef Shiloh (Tel Aviv University, Israel) described his extensive studies of the ATM protein, which is defective in the neurodegenerative and cancer-prone syndrome ataxia telangiectasia. ATM controls signaling networks by phosphorylation of key players in response to DNA-strand breakage; it is a transducer, interacting with initial DNA-damage sensors. Two interesting new substrates of ATM were described by Shiloh. One is the COP9 signalosome, a large and essential eight-subunit protein complex that resembles a component of the proteasome. The other is KAP-1, a general transcription co-repressor. These results, as well as data suggesting that strand-break repair activities, such as that mediated by the MRE-11 protein, can act both upstream and downstream of the ATM transducer in damage signaling, further complicate the proposals for DNA-damage signaling networks. A current model is that a DNA double-strand break rapidly mobilizes several ATM-independent proteins, including the minor histone variant H2AX. ATM protein is then recruited to the damage site to form a stable platform for further protein interactions in the damage response. An upcoming comprehensive special issue of the journal *DNA Repair*, guest-edited by Shiloh, summarizes the current state of the field.

New results on the array of nucleosomes that form a chromatin fiber were presented by Tim Richmond (Swiss Federal Institute of Technology, Zurich, Switzerland) and Daniela Rhodes (Medical Research Council Laboratory of Molecular Biology, Cambridge, UK). Richmond has proceeded in a logical way from his high-resolution structure of the nucleosome core particle to defining the structure of a two-start helix in the chromatin fiber, which he has so far done without the extra complication of bound histone H1. Rhodes has systematically investigated the reconstitution of a chromatin fibre, using a repeated DNA sequence that is less heterogeneous than the more commonly employed 5S DNA sequence. Pilot experiments by cryo-electron microscopy indicate that a 177 base-pair repeat length was optimal, and a stable, soluble and compactly folded structure of 22 such DNA repeats was obtained in the presence of histone H5 (the chicken version of H1). More detailed chromatin fibre structures obtained by a combination of X-ray crystallography and electron microscopy can now be eagerly anticipated.

Susan Gasser (University of Geneva, Switzerland) described the intricate nuclear arrangement of specific DNA sequences in the G1 cell nucleus. Nuclear DNA is not just randomly distributed as in a bowl of spaghetti. Instead, chromosomes that are rich in genes, such as human chromosome 19, are centrally located in the interphase nucleus, whereas gene-poor chromosomes are located at the periphery. Telomeres are perinuclear and reversibly paired, and centromeres cluster opposite the nucleolus. Moreover, different chromosomal sites are under different levels of spatial constraint. Research on the nuclear matrix and nuclear organization has made rather slow progress in recent years, but there now appears to be a quantum jump in sophistication thanks to new and powerful technology and insightful experiments on the sub-structure of the cell nucleus. The presentations at the symposium showed that we are making impressive progress towards understanding the cell's response to DNA damage, and we can look forward to further exciting developments in the near future.