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Meeting report

2nd German-French DNA repair meeting – DNA damage and repair in ageing and degenerative diseases, Konstanz, Germany, September 20–23, 2009

Alexander Bürkle *, Alain Sarasin, Lisa Wiesmüller

Department of Biology, Box X911, University of Konstanz, 78457 Konstanz, Germany
Laboratory of Genetic Stability and Oncogenesis, CNRS UMR8200, Institut Gustave Roussy, University Paris-Sud, 94805 Villejuif, France
Department of Obstetrics and Gynaecology, University of Ulm, Prittwitzstr. 43, 89075 Ulm, Germany

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ABSTRACT

In September 2009, the French Society of Genetic Toxicology and the German Society for Research on DNA Repair jointly organized the '2nd German-French DNA repair meeting – DNA damage and repair in ageing and degenerative diseases', which was held in Konstanz, Germany. Here we summarize the content of the oral presentations given in the various scientific sessions and of prize-winning posters.

After the great success of the first joint scientific meeting of the French Society of Genetic Toxicology (www.sftg.org) and the German Society for Research on DNA Repair (www.dgdr.de) in Toulouse, France, in 2007 the two societies decided to jointly organize a second meeting, which was held in Konstanz, Germany, September 20–23, 2009. Although the Konstanz meeting was open to presentations of any kind of scientific activity in DNA repair research, the meeting had a focus on "*DNA Damage and Repair in Ageing and Degenerative Diseases*". This choice was very successful because among the 126 participants it attracted there were a good number of scientists from the field of biogerontology who had never attended previous meetings of the two societies. Furthermore, although it was organized by two national societies, participants came from many more countries, thus turning it into an international event. These two facts fostered scientific exchange and new contacts very much. Other very positive and encouraging aspects were (i) the strong representation of female speakers, especially among the presenters of proffered papers, which had been selected by the Scientific Committee based on anonymized abstracts, and (ii) the large number and high quality of posters presented. In the following paragraphs we summarize the content of the oral presentations in the various scientific sessions.

1. Keynote lecture and public lecture

The *keynote lecture* was given by *Jan Hoeijmakers* (Rotterdam, The Netherlands). It was entitled "Aging, DNA repair and cell death" and covered an impressive range of experimental approaches. He started out by recapitulating that DNA damage is a classical trigger of mutations, which may lead to cancer, but can also induce cell death or senescence, which may contribute to aging. The latter is the main tenet of the DNA Damage Theory of Aging. In order to antagonize accumulation of DNA damage DNA repair systems have evolved. Hoeijmakers and colleagues have focused on nucleotide excision repair (NER), which is organized in two modes, *i.e.* Global Genome NER, which prevents mainly mutations (and thereby cancer) and is deficient in some forms of Xeroderma pigmentosum (XP). (ii) In contrast, Transcription-Coupled Repair (TCR) selectively removes damage that obstructs transcription, thus counteracting cytotoxic effects of DNA injury (thereby delaying aging). Clinical examples are Cockayne syndrome (CS) and trichothiodystrophy (TTD), two syndromes featuring signs of premature aging features yet without cancer susceptibility. Strikingly, mutations in the NER helicases XPB and XPD can cause all three disorders or combinations thereof. Hoeijmakers showed that different single and double mouse NER mutants exhibit growth deficit, neurodegeneration, osteoporosis, early loss of fertility, premature aging of liver and kidney, deafness, retinal photoreceptor loss, depletion of hematopoietic stem cells, and a moderate or even dramatic reduction of life span. There was a strong correlation between the severity of repair defects and the severity of premature aging, in support of the

* Corresponding author. Tel.: +49 7531 884035; fax: +49 7531 884033.
E-mail address: Alexander.Buerkle@uni-konstanz.de (A. Bürkle).

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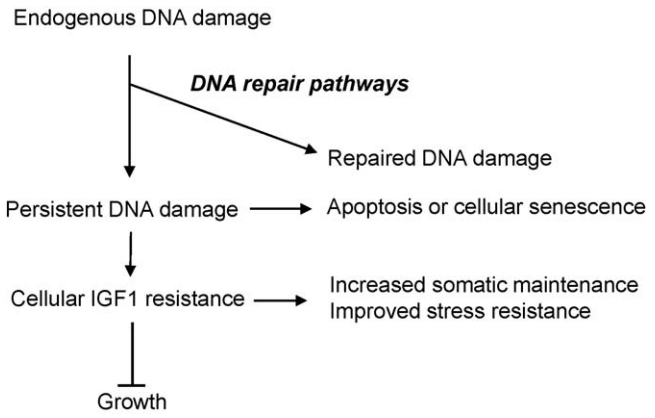

Fig. 1. Simplified scheme on the implication of unrepaired DNA damage in the aging process. Inverted T, blockage. For details, see text.

DNA-damage theory of aging. Strikingly, conditional mouse mutants display organ-specific accelerated aging, including targeted neurodegeneration in specific parts of the brain. In summary, endogenous DNA lesions recognized by NER pathways can hamper transcription/replication thus triggering apoptosis and premature aging. Importantly, persisting DNA damage suppresses the somatotrophic axis and up-regulates defenses, thus favoring maintenance at the expense of growth, a phenomenon similar to caloric restriction, which is known to promote longevity in many species (Fig. 1).

The public lecture was delivered by *Vilhelm A. Bohr* (Baltimore, MD, USA) and was entitled "DNA repair in aging and degenerative disease". In the first part of his lecture he addressed the Mitochondrial Theory of Aging, which can be viewed as an extension to Denham Harman's Free Radical Theory of Aging. The Mitochondrial Theory suggests that the mitochondrial decline with aging is due to mitochondrial DNA damage accumulation and is causative of many of the aging features. While all oxidation of macromolecules may be important, oxidative modification of DNA may be the most harmful to the organism. Thus, removal of oxidative DNA damage is a key defense process, and, similar to the situation in the nucleus, some mitochondrial DNA repair pathways exist to keep the steady-state level of damage low. However, the classical NER, described above, is not active in mitochondria. In the second part of his presentation, Bohr discussed human progeroid syndromes as these conditions have proved to be very suitable model systems for the study of aging. These diseases include Werner syndrome (WS), Bloom syndrome, Rothmund–Thomson syndrome, CS and others. An increasing number of proteins that are deficient in human progeroid syndromes seem to play roles in DNA repair. Bohr and his colleagues focused on the Werner syndrome protein (WRN) and other RecQ helicases and characterized interactions with major DNA double-strand break repair and BER proteins. Recently, they reported a physical and functional interaction between WRN and NEIL1 glycosylase. Their current data indicate that another RecQ helicase, the Rothmund–Thomson protein (RecQ 4) is also involved in these DNA repair pathways. Another important protein that antagonizes premature aging is CSB. This protein also interacts with base-excision repair (BER) proteins including NEIL1.

2. DNA repair, ageing and age-related diseases

Hartmut Geiger (Ulm, Germany) investigates DNA damage responses in the aged hematopoietic stem cell system in the mouse, in order to unravel the mechanisms underlying the well-known fact that cancer in general is a disease tightly associated with aging. He could show that hematopoietic progenitor cells, but not hematopoietic stem cells, from aged mice are more resistant to DNA damage compared to cells from young animals. Thus, the more likely cancer-initiating cell in age-related cancer could be a hematopoietic progenitor cell. Furthermore, he showed that the mutation frequency upon DNA damaging treatment does not increase in hematopoietic cells in aged animals and concluded that not only DNA mutations but distinct additional mechanisms might be the driving force in age-related cancer. A likely candidate is epigenetic modifications of DNA.

In general, all biological macromolecules including DNA, RNA, proteins, lipids and polysaccharides can undergo molecular damage, but repair activities have almost exclusively been described for DNA. The only exception is repair of a very specific kind of protein damage, *i.e.* oxidation of methionine residues leading to methionine sulfoxide formation, which was the topic of the presentation by *Bertrand Friguet* (Paris, France). Such protein damage can be reversed by the methionine sulfoxide reductase MsrA and MsrB. The Msr system has been implicated as an activity contributing to increased longevity and resistance to oxidative stress in different cell types and model organisms. Msr activity and expression of MsrA decrease with age *in vivo*, and both MsrA and MsrB2 are downregulated during cellular senescence. Friguet showed that overexpression of MsrA or MsrB2 in transfected cells leads to lower levels of protein oxidative damage and protects against oxidative stress-induced cell death. Interestingly, he could show that Msr overexpression also leads to lower level of intracellular ROS under oxidative stress conditions and protected both mitochondrial integrity and proteasome function against oxidative stress-induced inactivation. Viewed together it is exciting to see how major biochemical pathways/systems that are all tightly linked to the aging process, such as mitochondria, the cellular redox balance and the proteasome, are all responsive to interventions targeted at repair of oxidative protein damage.

Björn Schumacher (Cologne, Germany) focused on the role of persistent transcription-blocking DNA damage in the aging process. He showed that persistent DNA damage in primary cells elicits similar changes in global gene expression as those occurring in various organs of naturally aged animals. As is the case in aging animals, the insulin-like growth factor 1 (IGF-1) receptor and growth hormone receptor expression is attenuated under these conditions, resulting in cellular IGF-1 resistance. This cell-autonomous attenuation is specifically induced by persistent lesions that lead to RNA polymerase II stalling. It is detectable in proliferating, quiescent and terminally differentiated cells, and is exacerbated and prolonged in cells from progeroid mice and confers resistance to oxidative stress. He concluded that DNA damage accumulation in transcribed genes contributes to the aging-associated shift from growth to somatic maintenance that triggers stress resistance and is thought to antagonize tumorigenesis and promote longevity (Fig. 1).

Sylvie Sauvaigo (Grenoble, France) described a multiplexed excision/synthesis assay to examine simultaneously BER and NER capacities. She tested human primary fibroblasts derived from healthy donors of various ages and investigated changes in DNA repair attributed to chronic sun exposure, by comparing fibroblasts from sun-exposed and sun-protected sites of the same donors. She observed a marked age-related decrease of excision/synthesis repair whatever the repair pathway considered. Interestingly enough, distinct decline profiles were observed according to the nature of the base lesion studied. Cells from middle-age donors exhibited sun-exposure related adaptive up-regulation of repair activity of 8-oxoguanine and abasic sites. By contrast, cells from sun-exposed sites of elderly donors displayed significantly lower repair capacity than cells from sun-protected sites for these latter