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Indo-US workshop on base excision DNA repair, brain function and aging

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1. Background

A connection between DNA repair and lifespan was first proposed by Hart and Setlow, nearly 40 years ago (Hart and Setlow, 1974). At the time, most DNA damage was thought to be caused by environmental sources, such as UV, ionizing radiation and various chemicals. In the early 1970s, base excision DNA repair (BER) was just emerging as a newly-recognized pathway of DNA repair (Lindahl, 1974), although most of the target lesions for this system were as yet unknown. In the meanwhile, many additional DNA glycosylases have been discovered and their specificity recognized to include a large variety of deaminated, oxidized and alkylated bases (Svilar et al., 2011). In parallel, we now realize that DNA endures a considerable amount damage that arises from endogenous sources, ranging from the hydrolytic decay that deaminates cytosine to uracil or releases purine bases (Lindahl, 1993), to reactive metabolites and by-products that generate oxidized bases and abasic sites, as well as alkylated and other adducted species (Barnes and Lindahl, 2004). The prevailing view now is that this incessant onslaught, which threatens to degrade the functions of the genome, is in large part counteracted by the activities of BER (Svilar et al., 2011). Indeed, unlike the basic activities of nucleotide excision repair (Sancar et al., 2004) that had been correlated with lifespan (Hart and Setlow, 1974), the core BER functions are essential for viability, even at the cellular level (Svilar et al., 2011).

Much of the normal aging process affects cells that are not undergoing active proliferation, including neuronal cells (Kirkwood, 2005; Holliday, 2006). Even when the nuclear genome is not being duplicated, however, the replication of mitochondrial DNA continues unabated (Copeland, 2012). Continued mitochondrial function is essential for many cell types, in particular neurons. Yet mitochondria are also the locus of oxidative metabolism to generate

ATP, which localizes the potential for oxygen radicals in close proximity to mitochondrial DNA. Against this problem, the maintenance of mitochondrial function depends on functional DNA repair systems, which appear to be more limited in mitochondria than in the nucleus of mammalian cells (de Souza-Pinto et al., 2008; Liu and Demple, 2010). Although nucleotide excision repair, which operates on bulky lesions such as photodimers, does not seem to function in mitochondria, BER is well represented (Liu and Demple, 2010). Several DNA glycosylases are present in the mitochondria of human cells, as is the machinery to carry out both “classical” (single-nucleotide) BER and long-patch (multinucleotide) BER. Thus, it seems likely that BER processes are important to the functional maintenance of even terminally differentiated cells, and that BER in mitochondria will be found to contribute importantly to lifespan.

With this background in mind, we organized a workshop (Base Excision DNA Repair, Brain Function and Aging) to bring together scientists from India and the United States whose work touches on this topic. The meeting, which was held in January 2011 in Hyderabad, India, included about equal numbers of Indian and American scientists who presented their work to a focused audience that included Indian students and other researchers, and some science officials. The conference was inaugurated with an opening ceremony presided over by Prof. V. Kannan, Pro-Vice Chancellor, the University of Hyderabad. Words of welcome and encouragement were presented by Prof. D.N. Reddy, the Vice Chancellor of the Jawaharlal Nehru Technological University in Hyderabad. Their comments indicated the importance of this meeting at both the local and the national level. Prof. Kalluri Subba Rao and Dr. Vilhelm A. Bohr welcomed the 48 attendees of the meeting and other participants at the ceremony.

There then followed seven scientific sessions over two days, three of which opened with an Ellison Medical Foundation Lecture. The first of these, the opening scientific lecture of the meeting, was given by Prof. George M. Martin of the University of Washington, Seattle, titled “How important are stochastic variations in gene expression in explaining intra-specific differences in the pace and patterns of aging?” This presentation helped to frame some important general questions that were touched on by many other speakers throughout the rest of the meeting. His thoughts are developed further in the first paper of this issue, “Stochastic Modulations of the Pace and Patterns of Ageing: Impacts on Quasi-Stochastic Distributions of Multiple Geriatric Pathologies”.

The second Ellison Lecture was given by Prof. Lawrence A. Loeb of the University of Washington, Seattle, discussing “A mutator phenotype in cancer: mutations by base excision DNA repair”. This subject and further ideas about the contribution of mutations in somatic cells to the aging process and neurodegeneration and presented in his article in this issue, “Somatic Mutations in Aging, Cancer and Neurodegeneration”. The third Ellison Lecture was given by Prof. Vilhelm A. Bohr of the National Institute on Aging, Baltimore, titled “BER defects in human premature aging”. He develops this theme specifically for mitochondria in his article in this issue, “Repair of persistent strand breaks in the mitochondrial genome”.

The other articles in this special issue cover most of the range of subjects presented at the conference. In addition, the final meeting program is shown in the following pages. Lively question sessions followed each of the talks, and ample time for formal and informal discussion was included throughout the meeting.

A number of postdoctoral fellows and students from Indian laboratories participated in the meeting. They showed posters of their research work during breaks between the oral session, and they asked good questions of the speakers during the sessions. There was an excellent spirit of exchange and positive dynamics, and based on the mutual feeling that this area of research is rapidly growing and ripe for future advances and international collaboration, it was decided to plan another meeting of this kind in the near future.

References

- Barnes DE, Lindahl T. Repair and genetic consequences of endogenous DNA base damage in mammalian cells. *Annual Review of Genetics*. 2004; 38:445–476.
- Copeland WC. Defects in mitochondrial DNA replication and human disease. *Critical Reviews in Biochemistry and Molecular Biology*. 2012; 47(1):64–74. [PubMed: 22176657]
- de Souza-Pinto NC, Wilson DM 3rd, Stevnsner TV, Bohr VA. Mitochondrial DNA, base excision repair and neurodegeneration. *DNA Repair (Amst)*. 2008; 7(7):1098–1109. [PubMed: 18485834]
- Hart RW, Setlow RB. Correlation between deoxyribonucleic acid excision repair and life-span in a number of mammalian species. *Proceedings of the National Academy of Sciences of the United States of America*. 1974; 71(6):2169–2173. [PubMed: 4526202]
- Holliday R. Aging is no longer an unsolved problem in biology. *Annals of the New York Academy of Sciences*. 2006; 1067:1–9.
- Kirkwood TB. Understanding the odd science of aging. *Cell*. 2005; 120(4):437–447. [PubMed: 15734677]
- Lindahl T. An N-glycosidase from *Escherichia coli* that releases free uracil from DNA containing deaminated cytosine residues. *Proceedings of the National Academy of Sciences of the United States of America*. 1974; 71(9):3649–3653. [PubMed: 4610583]
- Lindahl T. Instability and decay of the primary structure of DNA. *Nature*. 1993; 362(6422):709–715. [PubMed: 8469282]
- Liu P, Demple B. DNA repair in mammalian mitochondria: much more than we thought? *Environmental and Molecular Mutagenesis*. 2010; 51(5):417–426. [PubMed: 20544882]
- Sancar A, Lindsey-Boltz LA, Unsal-Kacmaz K, Linn S. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. *Annual Review of Biochemistry*. 2004; 73:39–85.
- Svilar D, Goellner EM, Almeida KH, Sobol RW. Base excision repair and lesion-dependent subpathways for repair of oxidative DNA damage. *Antioxidants & Redox Signalling*. 2011; 14(12):2491–2507.