Published in final edited form as:

Mech Ageing Dev. 2011 August ; 132(8-9): 353–354. doi:10.1016/j.mad.2011.07.006.

3rd International Genome Dynamics in Neuroscience Conference: “DNA repair and neurological disease”

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Effective genotoxic stress responses are essential for development of the nervous system, as defects in DNA repair factors can lead to human diseases characterized by neuropathology (Caldecott, 2008; McKinnon, 2009; Jeppesen et al., 2011; McKinnon and Caldecott, 2007). In many cases the neurological defects are the most detrimental aspects of these diseases, and can involve neurodegeneration, neurodevelopmental disorders or brain tumors. Although these disorders have been linked to genomic alterations and diminished DNA repair capacity, the underlying molecular bases remain unclear. Additionally, defective DNA repair in mature neural tissues has been implicated in aging and recently to common neurodegenerative syndromes such as Alzheimer's disease and Parkinson disease (Bender et al., 2006; Lu et al., 2004; Nospikel and Hanawalt, 2003). This suggests that the increasing size of the aging population will mean a surge of patients with these and other neurodegenerative disorders. Understanding how defective DNA repair impacts the nervous system will provide a means for developing therapies to address the resultant neurological problems.

The stability of genomes is constantly challenged by DNA damage induced by endogenous and exogenous agents, as well as spontaneous genome instability, recombination and stress responses. The nervous system is very sensitive to DNA damage, particularly in comparison to other non-proliferating tissues. In considering inherited human DNA repair deficiency syndromes the nature and source of endogenous DNA damage become important issues. One source of genomic damage is the rapid cellular proliferation that occurs during development that promotes replication-induced DNA damage. DNA repair, particularly non-homologous end-joining and single-strand break repair/base excision repair, also remain extremely important for homeostasis after cell proliferation ends and neural maturation commences, as evident by findings from mouse models of DNA repair deficiency (Barnes et

al., 1998; Gao et al., 1998; Lee et al., 2009; Shull et al., 2009). The brain metabolizes around 20% of consumed oxygen, but contains a relatively low capacity to neutralize reactive oxygen species, suggesting increased genomic lesions from free radical production (Barzilai, 2007; Karanjawala et al., 2002). Because neurons are particularly susceptible to oxidative stress these conditions conspire to threaten genome stability in the nervous system. Moreover, as the mitochondrial (mt) genome is located at the inner mitochondrial membrane, which is a major site of ROS generation, mtDNA damage can readily occur (de Souza-Pinto et al., 2008; Detmer and Chan, 2007; Schon and Przedborski, 2011). Compromised mitochondrial function has been linked to neurodegeneration including Alzheimer's and Parkinson's disease (Bender et al., 2006; de Souza-Pinto et al., 2008; Weissman et al., 2007). Furthermore, oxidative stress has been implicated in neurodegenerative diseases involving triplet expansions that can lead to e.g. polyglutamine tract expansion via error-prone repair which increases repeat expansions towards disease levels (Kovtun et al., 2007). Understanding the impact of genome instability and DNA repair mechanisms requires an interdisciplinary approach of molecular biology, physiology, imaging and clinical medicine.

The Genome Dynamics in Neuroscience conference series was established as a platform for integrating basic processes of DNA damage signaling and repair and clinical aspects of neurological and neurodegenerative disease. This conference series was initiated in 2006 by Vilhelm Bohr (NIH/NIA), Tone Tonjum, and Ole Pettersen (University of Oslo), resulting in the first Genome Dynamics in Neuroscience meeting in Oslo, Norway, April 26–29, 2006. The second conference was organized by Cynthia McMurray (Mayo Clinic) and George Martin (University of Washington) and was held on June 13–17th, 2008 at the Asilomar Conference Grounds in Pacific Grove, California, USA, and focused on DNA Transactions in the Aging Brain.

The 3rd Genome Dynamics in Neuroscience meeting was held at the Hilton Metropole in Brighton, UK, from July 18–21, 2010 and was organized by Keith Caldecott (University of Sussex), Peter McKinnon (St Jude Children's Research Hospital), and Vilhelm Bohr (National Institute Aging). The objective of the meeting was to highlight key aspects of DNA damage and repair in the developing and mature nervous system and how this prevents neurological disease, with a focus on addressing the medically relevant gaps that exist in our understanding of the connections between faulty DNA repair and dysfunction of the nervous system. Topics addressed covered the basic biology of DNA repair in neurons, synaptic plasticity, the pathogenesis of neurodegenerative disorders, nuclear and mitochondrial genome stability, stem cell biology, and brain development. The program brought together leading scientists with primary interests in DNA damage signaling together with those working in related areas of neurodegenerative disease. The theme of DNA repair and genomic instability is most often discussed at meetings in the context of proliferating cells and cancer. However, it is becoming clear that the impact of lesions in differentiating or terminally differentiated cells such as neurons is important in pathologies associated with aging, and the Program aimed to address this. The Meeting opened on Sunday evening (July 18th) with keynote addresses from Profs Jan Hoeijmakers (Erasmus University, Holland) and Malcolm Taylor (University of Birmingham, UK). Sessions ran from Monday morning for 2 full days (platform and poster), and finished after a morning session on Wednesday.

The meeting was divided into focus sessions that covered DNA repair pathways that maintain brain development and specific sessions on spinocerebellar ataxias, triplet expansion diseases, neural cell fate, mitochondria, and ageing in the brain. This conference successfully promoted interactions between the communities of investigators with interests in basic research on brain aging, DNA repair of nucleic acids, and research on specific neurodegenerative disorders.

In this Special issue selected reviews focus on the broad aspects of work presented at the Genome Dynamics meeting. Arne Klungland and Robert Lightowlers present their work examining mitochondrial function in the nervous system, while Mark Lovell and Tone Tonjum provide overviews of their respective work dealing with nucleic acid modifications in Alzheimer's Disease and base excision repair during human cognitive decline. Kalluri Subba Rao examines the utility of the comet assays in assessing DNA repair in the nervous system while Zixu Mao and Zhao-Qi Wang examine, respectively, the roles of Cdk5 and Nbsl in this context. Ari Barzilai reviews neuro-glial-vascular interrelations in genome instability syndromes and Vilhelm Bohr looks at glutamate stimulation of DNA repair. Laura Niedernhofer presents work focusing on age-related peripheral neuropathy and Cristina Montagna examines aneuploidy in the aging brain. Finally, Ubiquitin function in the brain is considered in articles by Thierry Nospikel and Mark O'Driscoll. These articles provide vignettes of the array of topics dealing with various aspects of genome stability in the nervous system that were covered during the 3rd Genome Dynamics in Neuroscience meeting. It was a very dynamic and stimulating meeting held in a pleasant venue close to the famous beach and piers in Brighton, UK. The excitement was also reflected in the decision to continue this series of meetings, and the next one will take place in Oslo, Norway in 2012.

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