Plenary Session Proposal

SfRBM 2018 Meeting

Submitted by:

Professor Clare Hawkins Department of Biomedical Sciences University of Copenhagen Panum, Blegdamsvej 3, Copenhagen, DK-2200, Denmark Email: clare.hawkins@sund.ku.dk	Professor Henrik Poulsen Laboratory of Clinical Pharmacology Q Rigshospitalet Blegdamsveg 9, Section Q7642 Copenhagen, DK-2100, Denmark Email: hepo@rh.dk

Session Chairs: Clare Hawkins, Henrik Poulsen

Topic: Regulatory role of RNA / DNA oxidation and its functional significance in disease

Background: Historically, the formation of oxidized or modified nucleobases within RNA and DNA during oxidative stress is generally regarded as detrimental to cellular processes, as the correct functionality of proteins is critically dependent on the presence of unaltered RNA and DNA. Indeed, the formation of modified nucleobases *in vivo*, particularly 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), is strongly linked to mutations and decreased gene transcription. This culminates in cellular dysfunction and death and has been implicated in the development of cancer, diabetes, atherosclerosis and neurodegenerative disease. However, there is increasing evidence to support a regulatory role of DNA oxidation. Recent advances in the development of labelling approaches to selectively enrich and isolate nucleic acids containing oxidized guanine have allowed the sequencing of 8-oxodG containing genomes, which supports a new role of DNA oxidation as an epigenetic modification. Also, incorporation of 8-oxodG into DNA from the nucleotide pool versus via direct oxidation of the DNA, is now recognised to differentially modulate cellular outcomes. This is highlighted in recent studies showing a dual role of this modified lesion in the regulation of telomerase activity. This symposium will highlight recent advances the newly discovered regulatory and epigenetic implications of 8-oxodG formation, together with discussing the functional significance of RNA oxidation, including the quality control measures for oxidized RNA and the role of 8-oxo-7,8-dihydro-guanosine (8-oxoGuo) as a diagnostic marker in human disease.

Title: Mapping the genome for oxidatively modified DNA

Speaker: Professor Cynthia Burrows
Department of Chemistry, University of Utah
315 South 1400 East, Salt Lake City,
Utah 84112-0850, USA
E-mail: burrows@chem.utah.edu
URLs: https://chem.utah.edu/directory/burrows/

Cynthia Burrows is a Distinguished Professor and Thatcher Presidential Endowed Chair of Biological Chemistry within the Department of Chemistry at the University of Utah. Her research is focused on nucleic acid chemistry, with a focus on chemical and oxidative modifications to DNA and RNA bases. This is of interest primarily as such modifications are typically deleterious leading to mutations, genetic diseases and cancer. Prof Burrows has recently developed a novel chemical labelling approach to enable the sequencing of the mouse genome for oxidatively modified DNA. She has demonstrated that oxidation of DNA to yield 8-oxo-7,8-dihydroguanine in gene promoters can act as a signalling agent for gene activation, and has provided direct evidence that this type of modified DNA lesion can represent an epigenetic modification.

References (1) Ding Y, Fleming AM, Burrows CJ. Sequencing the Mouse Genome for the Oxidatively Modified Base 8-Oxo-7,8-dihydroguanine by OG-Seq. J Am Chem Soc. 2017 Feb 22;139(7):2569-2572. doi: 10.1021/jacs.6b12604. PubMed PMID: 28150947; (2) Fleming AM, Ding Y, Burrows CJ. Oxidative DNA damage is epigenetic by regulating gene transcription via base excision repair. Proc Natl Acad Sci U S A. 2017 Mar 7;114(10):2604-2609. doi: 10.1073/pnas.1619809114. PubMed PMID: 28143930.

Title: Regulation of telomerase activity by oxidised DNA lesions

Speaker: Associate Professor Patty Opresko
Department of Environmental and Occupational Health
Hillman Cancer Center
University of Pittsburgh
5117 Centre Avenue, Suite 2.6a, Pittsburgh, PA 15213, USA
E-mail: plo4@pitt.edu
URLs: http://www.pitt.edu/~plo4/

Patty Opresko is an Associate Professor within the Department of Environmental and Occupational Health, University of Pittsburgh. Her research is focused on understanding the molecular mechanisms of genomic instability associated with cancer and aging, particularly in relation to telomeric DNA, including the genetic and environmental factors that alter rates of telomere attrition, and the cellular pathways that repair and restore damaged telomeric DNA. She is the recipient of numerous project grants, and has chaired sessions at DNA damage and repair focused Gordon Conferences. In recent studies published in Nature Structural and Molecular Biology, she has demonstrated that the oxidised DNA base, 8-oxo-7,8-dihydro-2'-deoxyguanine, has a dual role in inhibiting or stimulating telomerase, which has a significant effect on the biological outcome, and implications for the development of cancer.

Reference Fouquerel E, Lormand J, Bose A, Lee HT, Kim GS, Li J, Sobol RW, Freudenthal BD, Myong S, Opresko PL. Oxidative guanine base damage regulates human telomerase activity. Nat Struct Mol Biol. 2016 Dec;23(12):1092-1100. doi: 10.1038/nsmb.3319. PubMed PMID: 27820808.

Title: Cellular consequences and repair of oxidised RNA

Speaker: Dr Hani Zaher
Department of Biology
Washington University in St Louis
St. Louis, MO, USA
E-mail: hzaher@wustl.edu
URLs: https://wubio.wustl.edu/zaher and http://pages.wustl.edu/zaher

Dr Hani Zaher is an Assistant Professor within the Department of Biology, Washington University at St Louis. His research is focused on understanding the functional role of RNA during the process of translation, which is important as the correct decoding of genomic information into functional protein sequences is essential for proper growth and cell viability. He has an interest in understanding how oxidative damage to RNA affects the cellular quality control pathways, particularly ribosome-based mRNA pathways. This is significant in light of data showing that oxidation of RNA can have dramatic effects of protein synthesis, and is increasingly linked with the development of human disease.

Reference: Simms CL, Zaher HS. Quality control of chemically damaged RNA. Cell Mol Life Sci. 2016 Oct;73(19):3639-53. doi: 10.1007/s00018-016-2261-7. PubMed PMID: 27155660.

Title: Oxidative stress to RNA/DNA in the clinical setting: clinical intervention trials and epidemiology

Speaker: Professor Henrik Poulsen
Laboratory of Clinical Pharmacology Q
Rigshospitalet, Blegdamsvej 9, section Q7642
DK-2100 Copenhagen, Denmark
E-mail: hepo@rh.dk
URLs: http://www.cpnc.dk/

Henrik E. Poulsen M.D. is full professor in Clinical Pharmacology at the University of Copenhagen. He has been active in studies of the guanine modifications in DNA and RNA for more than 25 years, and has made pivotal developments in the analysis of oxidized DNA and RNA and the use of urinary excretion of 8-oxo-deoxy-Guanosine and 8-oxo-Guanosine in human studies. He has authored more than 350 papers, and has conducted several controlled, randomized clinical trials on oxidative stress, and also large epidemiological cohort studies. Prof. Poulsen has demonstrated that oxidative stress, measured as RNA oxidation, is highly predicative for death in patients with type 2-diabetes. His latest and unpublished work is focussed on large cohort studies of normal people, with several papers in press on the topics of factors that determine the level of oxidative stress and the consequences, following the strategy of translational research.

Reference: Laura K. Kjær, Vanja Cejvanovic, Trine Henriksen, Kasper M. Petersen, Torben Hansen, Oluf Pedersen, Cramer K. Christensen, Christian Torp-Pedersen, Thomas A. Gerds, Ivan Brandslund, Thomas Mandrup-Poulsen, and Henrik E. Poulsen, Cardiovascular and All-Cause Mortality Risk Associated With Urinary Excretion of 8-oxoGuo, a Biomarker for RNA Oxidation, in Patients With Type 2 Diabetes: A Prospective Cohort Study. Diabetes Care. 2017 Dec; 40(12):1771-1778. doi: 10.2337/dc17-1150. PMID 29061564.