Seminar

Ulrich Hübscher, Prof., Dr.med.vet.

Director of the Institute
Institute of Veterinary Biochemistry and Molecular Biology
University of Zürich-Irchel, Switzerland

„Oxygen as a friend and enemy: how to combat the mutational potential of 8-oxo-guanine“

Abstract:

The maintenance of genetic stability is of crucial importance for any form of life. Prior to cell division in each mammalian cell, the process of DNA replication must faithfully duplicate the three billion bases with an absolute minimum of mistakes. Various environmental and endogenous agents, such as reactive oxygen species (ROS), can modify the structural properties of DNA bases and thus damage the DNA. Upon exposure of cells to oxidative stress, an often generated and highly mutagenic DNA damage is 7,8-dihydro-8-oxo-guanine (8-oxo-G). The estimated steady-state level of 8-oxo-G lesions is about 103 per cell/per day in normal tissues and up to 105 lesions per cell/per day in cancer tissue. The presence of 8-oxo-G on the replicating strand leads to frequent (10-75%) misincorporations of adenine opposite the lesion (formation of A:8-oxo-G mispairs), subsequently resulting in C:G to A:T transversion mutations. These mutations are among the most predominant somatic mutations in lung, breast, ovarian, gastric and colorectal cancers. Thus, in order to reduce the mutational burden of ROS, human cells have evolved base excision repair (BER) pathways ensuring (i) the correct and efficient repair of A:8-oxo-G mispairs and (ii) the removal of 8-oxo-G lesions from the genome. Very recently we showed that MutY glycosylase homologue (MUTYH) and DNA polymerase λ play a crucial role in the accurate repair of A:8-oxo-G mispairs.

References:

1. van Loon, B., Markkanen, E. and Hübscher, U.: Oxygen as a friend and enemy: How to combat the mutational potential of 8-oxo-guanine. *DNA repair* **9**, 604-16, 2010.
2. Maga, G., Villani, G., Crespan, E., Wimmer, U., Ferrari, E., Bertocci, B. and Hubscher, U. 8-oxo-guanine bypass by human DNA polymerases in the presence of auxiliary proteins. *Nature* **447**, 606-8, 2007.
3. Maga, G., Crespan, E., Wimmer, U., van Loon, B., Amoroso, A., Mondello, C., Belgiovine, C., Ferrari, E., Locatelli, G., Villani, G., Hübscher, U.: Replication Protein A and Proliferating Cell Nuclear Antigen coordinate DNA polymerase selection in 8-oxo-G repair. *Proc. Natl. Acad. Sci. USA* **105**, 20689-20694, 2008.
4. van Loon, B. & Hubscher, U.: An 8-oxo-guanine repair pathway coordinated by MUTYH glycosylase and DNA polymerase lambda. *Proc Natl Acad Sci U S A* **106**, 18201-6, 2009.

The seminar will be held

on Tuesday 17. 5. 11 at 14.00

in the Milan Hašek Auditorium

(IMG AS CR, Vídeňská 1083, Prague 4).