The role and cooperation of AidB dehydrogenase and AlkB dioxygenase in repair of adducts to DNA and RNA bases

DNA of all living organisms is continuously exposed to damaging agents of exogenous and endogenous origin, but, fortunately, living beings are also well prepared to repair constantly occurring lesions. Recently, it was discovered that besides BER and NER pathways, where (generally speaking) damaged bases are removed and replaced, there is a new efficient repair mechanism involving AlkB-family dioxygenases. The AlkB-type dioxygenases are enzymes which remove only the modification from bases *via* a newly discovered oxidative mechanism which restore native DNA structure. The cellular 'production' of AlkB and three other proteins, including AidB dehydrogenase, is induced by low doses of the damaging agent, so that the cell is prepared to defend against a higher concentration of mutagens that may occur in the environment.

As a result of direct AlkB removal of base modifications, **toxic and mutagenic by-products are formed:** formaldehyde, glyoxal or malondialdehyde. Our studies indicate that AlkB is efficiently inhibited *in vitro* by the side products of the repair reaction.

The biological role and substrates of AidB are unknown. It is known that AidB does not repair DNA lesions, its crystallographic structure points to small molecule substrates. My preliminary studies have shown that *aidB*- mutant is more sensitive to glyoxal than the wild type strain. This allowed me to formulate a hypothesis that the **function of AidB dehydrogenase may be the detoxification of highly reactive by-products generated as a result of AlkB repair, and that to prevent their release to the cell, these enzymes can interact directly in the homeostasis maintenance.**

It is known that AlkB removes methylation damage from RNA. As part of this project, we will also **verify the biological significance of direct RNA repair by AlkB**.

Our studies are absolutely pioneering in the field of AidB dehydrogenase involving in nucleic acids repair and essential for better understanding of the newly discovered mechanism of DNA/RNA repair. The substrate specificity and the mechanism of action of AidB dehydrogenase is so far unknown. The phenomenon of repair of RNA base damage was described only for methylation modifications, which also occur naturally. On the other hand, we have discovered that AlkB removes also etheno- and hydroxypropanobridges both *in vitro* and *in vivo*. Proposed here research may lead to important discoveries. Proposed here studies are crucial to understanding the mechanisms by which the cell maintains homeostasis.

The planed studies are very important because issues concerning nucleic acids repair are essential for carcinogenesis and the lesions are indicators of the organisms' exposition to various environmental carcinogens. In longer perspective they may have an impact in development of medical diagnostics and anticancer therapy. Our results can also be a strong argument in discussion regarding the significance of direct RNA repair. Despite very promising data concerning repair of methylated RNA by AlkB-like enzymes, the potential importance of RNA demethylation needs further verification since RNA methylation occurs also naturally. Studied by us adducts to RNA bases do not play any biological role, so its repair may be a strong argument in the discussion concerning the importance of direct RNA repair. Unveiling the role of repair enzymes is the first step in searching of inhibitors and projecting drugs.

Results obtained in this project will help in planning future studies concerning other human and plant AlkB homologues involved in nucleic acids repair. Elucidation of molecular mechanism of action will contribute to a great extent to understanding the real nature of the so important, existing in all living organisms, enzymes.