invites to a seminar by

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Repair of the oxidatively damaged DNA in etiology and therapy of cancer

14th December 2017 at 12 p.m.

Venue: Centre of New Technologies, Banacha 2C,
Lecture Hall 0142 (Ground floor)

Host: Prof. Joanna Kargul

Oxidative stress, which arises during inflammations, infections and several metabolic pathways generates plethora of mutagenic DNA lesions, implicated in human pathologies, such as neurodegeneration or cancer. The major repair system removing oxidatively modified DNA bases is base excision repair (BER), in which DNA glycosylase recognizes and excises modified base, baseless phospho-sugar backbond (AP-site) is incised by AP-endonuclease, lacking nucleotide is incorporated by specific DNA polymerase, and free DNA ends are sealed by ligase. Using surrogate tissue, blood leukocytes from lung and colorectal cancer (CRC) patients and healthy controls we have found that oxidative DNA lesions, 8-oxoguanine (8-oxoGua), and lipid peroxidation-driven etheno-DNA adducts, 1,N^6-ethenoadenine (εA), and 3,N^4-ethenocytosine (εC) are elevated in cancer patients, but excision capacity for these lesions is decreased or similar to that of healthy controls. Differences in repair rate are related to the organ, in which cancer develops, as well as its histological type. In addition, oxidative stress status, namely low 8-oxoGua level in the DNA of blood leukocytes and in urine of CRC patients, as well as high level of uric acid, a potent reactive oxygen species (ROS) scavenger may be prognostic markers, since they correlate with longer survival of CRC patients.

Polymorphism of BER genes is often related to decreased activities of repair proteins and increased cancer risk. We have found that the frequency of 8-oxoGua DNA glycosylase 1 (OGG1) polymorphism Ser 326Cys is higher in CRC and lung cancer patients than in healthy controls, and Cys326Cys homozygotes have lower 8-oxoGua excision activity than Ser326Ser homozygotes and heterozygotes. Another factor, which may decrease excision of oxidatively damaged DNA bases is lipid peroxidation (LPO). One of the major LPO products, 4-hydroxynonenal (HNE) affects the balance of consecutive BER stages: excision of ε-adducts, but not 8-oxoGua is inhibited, AP-site excision is stimulated, but ligation is inhibited in cells exposed to HNE. This results in unfinished repair, and leaving strand breaks in the DNA exposed simultaneously to LPO and other genotoxic agents, the situation frequently met in living organisms during inflammations and infections.

In lung and colon tumor tissues excision rate of εA and εC, as well as 8-oxoGua in lung was significantly higher than that in histologically unchanged (normal) tissues. Such increased activity of BER proteins in tumor tissues might support cancer growth due to: (i) limitation of cancer cells genome instability under oxidative stress conditions, which might enable or prolong their survival; (ii) due to moonlight activities of several BER enzymes, namely, OGG1 and TDG glycosylases, APE1 endonuclease and poly(ADP-ribose) polymerase 1 (PARP1), regulate cell signaling. Our studies show that OGG1 and APE1 regulate expression of such genes as c-MYC, Bcl2, cyclin D and E1, and their polymorphic forms behave differently than wild type ones. Altogether these results suggest that increased oxidative stress and deregulated repair of oxidatively damaged DNA bases may be a driving force for the development of some, if not majority of human cancers.

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