revealed unanticipated heterogeneity of clinical features, between and within complementation groups [1]. Skin cancer is most common in XP-C, XP-E and XP-V patients, previously considered to be the milder groups based on cellular analyses. These patients have normal sunburn reactions and are therefore diagnosed later and are less likely to adhere to UV protection. XP-C patients are specifically hypersensitive to ocular damage, and XP-F and XP-G patients appear to be much less susceptible to skin cancer than other XP groups. Within XP groups, different mutations confer susceptibility or resistance to neurological damage [2]. Our findings on this large cohort of XP patients under long-term follow-up reveal that XP is more heterogeneous than has previously been appreciated. Our data now enable provision of personalized prognostic information and management advice for each XP patient, as well as providing new insights into the functions of the XP proteins.

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G. Spivak

TRANSCRIPTION-COUPLED REPAIR: AN UPDATE

Department of Biology, Stanford University, Stanford, California, USA

gspivak@stanford.edu

Nucleotide excision repair (NER) is a versatile pathway that removes helix-distorting DNA lesions from the genomes of organisms across the evolutionary scale, from bacteria to humans. NER involves recognition of lesions, adducts or structures that disrupt the DNA double helix, removal of a short oligonucleotide containing the offending lesion, synthesis of a repair patch copying the opposite undamaged strand, and ligation, to restore the DNA to its original form. Transcription-coupled repair (TCR) is a subpathway of NER dedicated to the repair of lesions that, by virtue of their location on the transcribed strands of active genes, encumber elongation by RNA polymerases. Mutations that result in null or reduced functionality of NER proteins cause mild to extreme photosensitivity in humans. Of particular interest are Cockayne and UV-sensitive syndromes: individuals with these diseases are proficient in NER but lack TCR of lesions that significantly distort the DNA double helix.

Smaller lesions, such as those caused by oxidation, are repaired by the base excision repair (BER) pathway. To elucidate whether a lesion resulting from oxidation of DNA, 8-oxo-Guanine, is subject to TCR, we developed an ultrasensitive approach combining single-cell electrophoresis (the comet assay) with fluorescent in situ hybridization (FISH) using strand-specific probes. The method allowed the quantification of low, physiologically relevant levels of specific DNA lesions in each strand of defined DNA sequences. We determined that 8-oxo-Guanine is preferentially repaired on the transcribed strand of the ATM gene in human cells, and this requires actively transcribing RNA polymerase II, CSB, UVSSA, hOGG1 and XPA, suggesting the participation of both BER and NER in this process [4].

I will review the biochemical pathways for TCR in the bacterium *Escherichia coli*, the yeast *Saccharomyces cerevisiae*, and human cells, and discuss how and when cells might choose to utilize TCR for repair and for restoration of transcription [1–5].

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M. Svetlova[1]*, L. Solovjeva[1], V. Kulikova[1, 2], K. Nerinovski[3], A. Yakimov[2, 4], A. Nikiforov[1]

STIMULATION OF NAD BIOSYNTHESIS ENHANCES THE EFFICIENCY OF DNA REPAIR IN HUMAN CELLS

[1] *Institute of Cytology RAS, St. Petersburg, Russia*
[2] *Peter the Great St. Petersburg Polytechnic University, St. Petersburg, Russia*
[3] *Department of Nuclear Physics Research Methods, St. Petersburg State University, St. Petersburg, Russia*
[4] *Petersburg Nuclear Physics Institute, NRC Kurchatov Institute, Gatchina, Russia*

*svetlma@mail.ru

Nicotinamide adenine dinucleotide (NAD) is one of the major coenzymes of redox reactions in central metabolic pathways. Moreover, NAD also serves as a substrate of several families of regulatory proteins such as protein deacetylases (sirtuins), ADP-ribosyltransferases and poly(ADP-ribose) polymerases (PARP), which govern many vital processes including cell response to genotoxic stresses. PARP1 is the major NAD consuming enzyme which is hyperactivated and auto-poly (ADP-ribosyl)ated in response to DNA strand breaks. It accumulates poly (ADP-ribose) (PAR) on chromatin at the sites of DNA damage and facilitates recruitment of DNA repair factors.

In this study we examined the effect of modulation of NAD levels on DNA strand break repair in human cells after genotoxic stresses.

First, we analyzed the effect of administration of NAD precursors on the level of NAD and DNA repair efficiency after the treatment of human dermal fibroblasts (HDF) and HEK293 cells with hydrogen peroxide (H_2O_2). Hyperactivation of PARP1 in response to oxidative stress led to a very fast and intensive accumulation of PAR in HEK293 cells and to a less PAR accumulation in HDF. Significant drop of NAD was observed after H_2O_2 treatment in both cell lines. Administration of NAD precursors (nicotinamide riboside, NR or nicotinic acid riboside, NAR) before and during treatment with H_2O_2 led to a partial recovery of NAD level. Effectiveness of DNA single strand