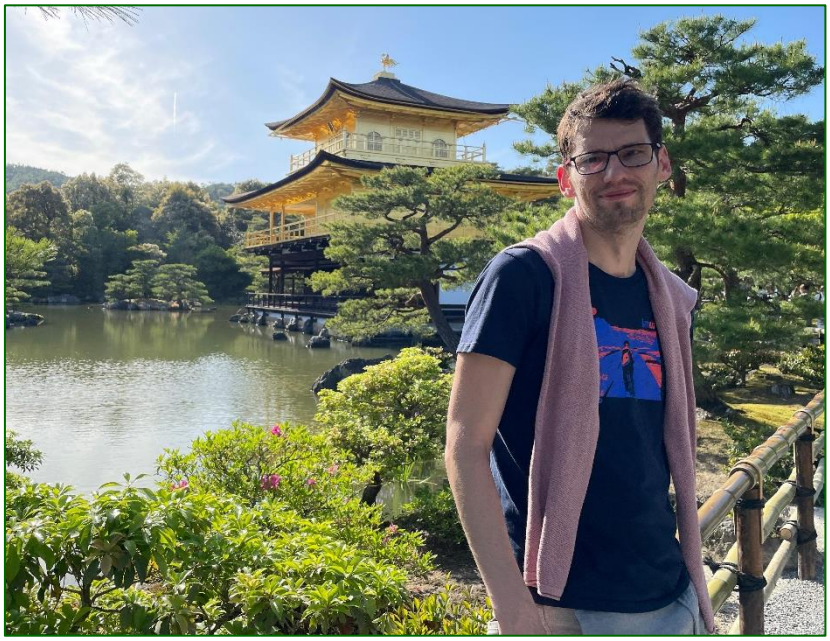
Univerzita Karlova

Přírodovědecká fakulta

KATEDRA BIOCHEMIE

ZVE NA SEMINÁŘ

MOLECULAR MECHANISMS AND ARCHITECTURE OF DNA INTERSTRAND CROSSLINK REPAIR



RNDr. Jan Šilhán, Ph.D.

(ÚOCHB AV ČR v.v.i., Praha)

PONDĚLÍ 03. 03. 2025 v 9:00

V posluchárně CH3 chemické sekce PřF UK, Hlavova 8, Praha 2

Hosté jsou srdečně zváni!

Program semináře, anotace přednášek:
natur.cuni.cz/chemie/katedry-a-pracoviste/katedra-biochemie/seminare/journal-club

Anotace

DNA interstrand crosslinks (ICLs) are toxic lesions that stall replication and transcription, necessitating specialized repair pathways to maintain genomic integrity. My research dissects the molecular architecture and enzymatic mechanisms underlying ICL repair, revealing how cells counteract these barriers.

We first focused on the mechanisms of the FA pathway; an array of genes responsible for DNA crosslink repair. Our previous biochemical studies on SLX4 uncovered its activation of XPF-ERCC1, directing specificity toward replication forks and facilitating ICL unhooking. We have shifted our focus to DNA crosslinks generated from alcohol metabolism, specifically acetaldehyde-induced ICLs (AA-ICLs). Our findings implicate the FA pathway as a major player in resolving AA-ICLs. We have now demonstrated that the Fanconi anaemia (FA) nuclease Slx4-Xpf-Ercc1 (SXE) executes precise dual incisions flanking AA-ICLs. This, along with its role in repairing other crosslinks, defines SXE as a key factor in ICL repair and tumour suppression.

Expanding beyond FA-dependent repair, we investigate the formation and repair of naturally occurring a basic-site ICLs (Ap-ICLs). We studied how the specialized NEIL3 glycosylase recognizes and excises these lesions, guided by its GRF zinc-finger domain, which preferentially binds replication forks. Structural studies of NEIL3's catalytic domain provided insights into lesion recognition and repair coordination.

By integrating structural biology with biochemical reconstitution, our work reveals the architectural principles governing ICL repair, advancing our understanding of genome maintenance and its implications for cancer and genetic disorders

Curriculum Vitae

Jan Šilhán is a team leader at the Institute of Organic Chemistry and Biochemistry in Prague. He earned his Master's degree and RNDr. in Biochemistry, followed by a PhD in Physical Chemistry (January 2009) from Charles University under the supervision of prof. Tomáš Obšil. He then pursued postdoctoral research at Imperial College London for over three years, followed by another three years in the laboratory of K.J. Patel at the Laboratory of Molecular Biology in Cambridge.