LABORATORY OF

CANCER BIOLOGY

Proteasome, cancer, protein degradation, cell cycle, survival

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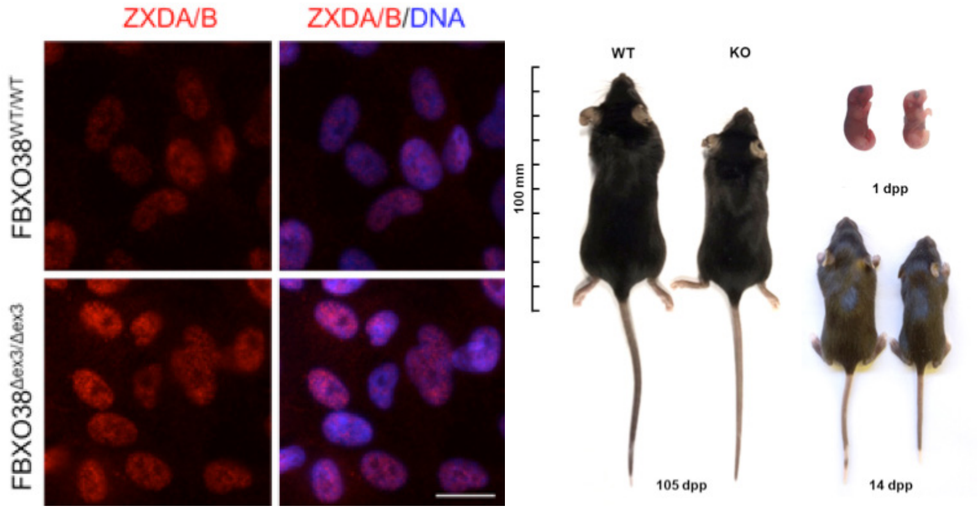
The primary function of the ubiquitin-proteasome system (UPS) is to degrade unnecessary or damaged proteins. Cullin-RING (CRL) ubiquitin ligases mediate the ubiquitination of many substrates. Our research focuses on discovering novel CRL substrates involved in cancer progression, stress response, or cell cycle. We anticipate that these novel interactions could serve as potential therapeutic targets in cancer and other pathological conditions. We are currently investigating the function of several CRL complexes.

Our main methodological approaches are:

- Biochemical analysis of CRL complexes and the discovery of their substrates and the signalling pathways that control their activity.
- Physiological aspects of CRLs function in the context of mammalian development.

In detail, we investigated the function of the F-box-containing protein 38 (FBXO38). FBXO38 is a substrate receptor for the SKP1-CUL1-dependent ubiquitin ligase (SCF). Several mutations in the FBXO38 gene have been found in patients with early distal hereditary motor neuronopathy, suggesting a role in nervous system homeostasis. Interestingly, another mutation was discovered when studying identical twins with discordant development of gender dysphoria. We identified ZXDA/B zinc finger proteins as its substrates. We further showed that ZXDA/B proteins are responsible for stabilizing centromeric chromatin and that FBXO38 negatively controls this process. Moreover, we investigated the physiological role of FBXO38 during mouse development. We found that FBXO38 controls the growth of several organs, including the testes, where it is expressed by Sertoli cells. Sertoli cells lacking FBXO38 exhibited impaired maturation, leading to improper stimulation of spermatogonia and impaired sperm production. This pathological process was accompanied by stabilization of the FBXO38 substrate ZXDB and changes in CENP-A/B positive centromeric regions.



(A) ZXDA/B is stabilized in FBXO38 KO cells. Wild-type (WT) or FBXO38 knockout RPE-1 cells (FBXO38•ex3/•ex3; KO) were grown on slides, fixed, and immunostained with the ZXDA/B antibody. DNA was stained with DAPI. Scale bar, 20 μm.
(B) Fbxo38 controls growth. Representative images of Fbxo38 WT and KO littermate males of indicated age. Dpp; days postpartum.

Selected publications:

1. Dibus N, Korinek V, Cermak L*. FBXO38 Ubiquitin Ligase Controls Centromere Integrity via ZXDA/B Stability. Front Cell Dev Biol. 2022 Jun 23;10:929288. doi: 10.3389/fcell.2022.929288. eCollection 2022. PMID: 35813202
2. Dibus N, Zobalova E, Monleon MAM, Korinek V, Filipp D, Petrusova J, Sedlacek R, Kasparek P, Cermak L*. FBXO38 Ubiquitin Ligase Controls Sertoli Cell Maturation. Front Cell Dev Biol. 2022 Jun 13;10:914053. doi: 10.3389/fcell.2022.914053. eCollection 2022. PMID: 35769260
3. Lidak T, Baloghova N, Korinek V, Sedlacek R, Balounova J, Kasparek P, Cermak L*. CRL4-DCAF12 Ubiquitin Ligase Controls MOV10 RNA Helicase during Spermatogenesis and T Cell Activation. Int J Mol Sci. 2021 May 20;22(10):5394. doi: 10.3390/ijms22105394. PMID: 34065512