LABORATORY OF

CANCER CELL BIOLOGY

Cancer, cell cycle, checkpoint, oncogene, tumour suppressor

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In the laboratory of Cancer Cell Biology, we study the cellular responses to genotoxic stress. We focus on the mechanisms that maintain genome integrity in healthy cells and on the defects that allow cancer cells to escape the surveillance mechanisms. In particular, we focus on protein phosphatase PPM1D/WIP1, which negatively regulates tumour suppressor p53. We employ cell biology, CRISPR-mediated gene editing, molecular biology and biochemical approaches to decipher the mechanisms that control the PPM1D/WIP1 function. In addition, we use mouse models to investigate the oncogenic properties of PPM1D/WIP1. We also explore PPM1D/WIP1 as a potential pharmacological target in cancers with wild-type p53. Finally, we screen cancer patients for mutations in cancer-predisposing genes to identify new prognostic biomarkers.

Figure 1. Working model for the role of PPM1D/Wip1 in cancer development | Upon genotoxic stress, healthy cells activate tumor suppressor p53 and stop transmission through cell cycle. Cells with abnormally high levels of PPM1D/Wip1 fail to stop in the checkpoint and continue proliferation despite the presence of damaged DNA. Accumulation of genetic abnormalities can eventually lead to cell transformation.

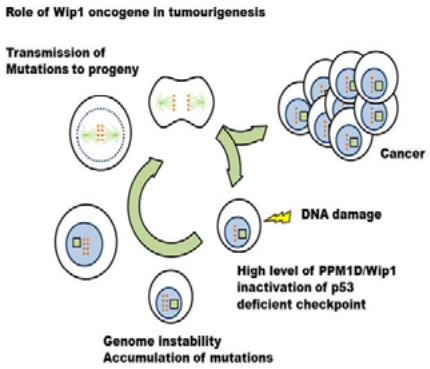


Figure 2. Mutation of PPM1D/Wip1 impairs cell cycle checkpoint | Healthy cells do not divide in the presence of DNA damage and arrest in G1 phase of the cell cycle (red). Cells carrying mutation in PPM1D gene continue progression through the cell cycle also in the presence of DNA damage and start replicating their genome (orange). Mutation in PPM1D does not affect cells in the G2 phase of the cell cycle.

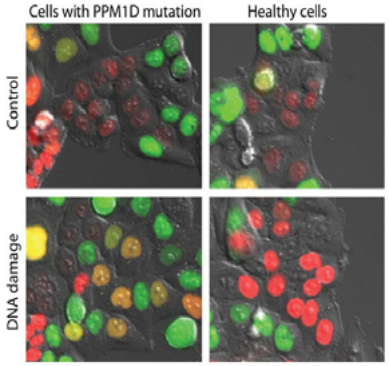
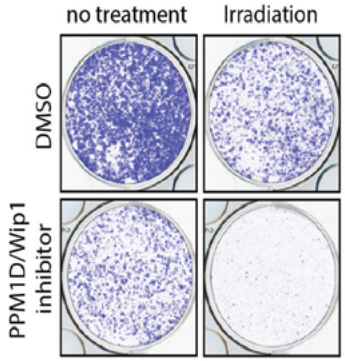


Figure 3. Suppression of cancer cell growth by combination of PPM1D/Wip1 inhibitor and radiotherapy | Breast cancer cells were treated or not with small-molecule PPM1D/Wip1 inhibitor and exposed to ionizing radiation. Colony formation (blue dots) was evaluated after 2 weeks.



Selected publications:

1. Burocziova M, Burdova K, Martinikova AS, Kasparek P, Kleiblova P, Danielsen SA, Borecka M, Jenikova G, Janečková L, Pavel J, Zemankova P, Schneiderova M, Schwarzova L, Ticha I, Sun XF, Jiraskova K, Liska V, Vodickova L, Vodicka P, Sedlacek R, Kleibl Z, Lothe RA, Korinek V, Macurek L (2019) Truncated PPM1D impairs stem cell response to genotoxic stress and promotes growth of APC-deficient tumors in the mouse colon. ***Cell Death Dis*, 10**:818.
2. Burdova K, Storchova R, Palek M, Macurek L (2019) WIP1 Promotes homologous recombination and modulates sensitivity to PARP inhibitors. ***Cells*, 8**:1258.
3. Jaiswal H, Benada J, Müllers E, Akopyan K, Burdova K, Koolmeister T, Helleday T, Medema RH, Macurek L, Lindqvist A (2017) ATM/Wip1 activities at chromatin control Plk1 re-activation to determine G2 checkpoint duration. ***EMBO J*, 36**:2161-2176.
4. Kleiblova P, Stolarova L, Krizova K, Lhota F, Hojny J, Zemankova P, Havranek O, Vocka M, Cerna M, Lhotova K, Borecka M, Janatova M, Soukupova J, Sevcik J, Zimovjanova M, Kotlas J, Panczak A, Vesela K, Cervenkova J, Schneiderova M, Burocziova M, Burdova K, Stranecky V, Foretova L, Machackova E, Tavandzis S, Kmoch S, Macurek L, Kleibl Z (2019) Identification of deleterious germline CHEK2 mutations and their association with breast and ovarian cancer. ***Int J Cancer*, 145**:1782-1797.

In the picture: 1. Gui Wentao | 2. Palek Matouš | 3. Karri Sirish | 4. Štorchová Radka | 5. Vieru Andra Stefania | 6. Aquino Perez Cecilia | 7. Císařová Natálie | 8. Macůrek Libor | 9. Pavel Jozef | 10. Stolařová Lenka