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BRCA1 or CDK12 loss sensitizes cells to CHK1 inhibitors

Statement of the Problem: A broad spectrum of tumors develops resistance to classic chemotherapy, necessitating the discovery of new therapies. One successful strategy exploits the synthetic lethality between poly (ADP-ribose) polymerase 1/2 proteins and DNA damage response genes including *BRCA1*, a factor involved in homologous recombination–mediated DNA repair and *CDK12*, a transcriptional kinase known to regulate the expression of *DDR* genes. Inhibitors of *CHK1* have been shown to enhance the anti-cancer effect of DNA-damaging compounds. Since, loss of *BRCA1* increases replication stress and leads to DNA damage, we tested a hypothesis that *CDK12*- or *BRCA1*-depleted cells rely extensively on S-phase-related *CHK1* functions for survival.

Methodology & Theoretical Orientation: We have utilized different approaches to examine effect of *CHK1* inhibitors in combination with down-regulated activity of *CDK12* and *BRCA1* on cell proliferation, survival, apoptosis, cell cycle and DNA-damage response pathway in various oncogenic cell lines and by employing a mouse orthotopic xenograft model.

Findings: The silencing of *BRCA1* or *CDK12* sensitized tumor cells to *CHK1* inhibitors *in vitro* and *in vivo*. *BRCA1* down-regulation combined with *CHK1* inhibition induced excessive amounts of DNA damage, resulting in an inability to complete the S-phase.

Conclusion & Significance: Therefore, we suggest *CHK1* inhibition as a strategy for targeting *BRCA1*- or *CDK12*- deficient tumors.

Biography

Jiri Kohoutek is broadly interested in regulation of transcription in eukaryotes. He is also focused to study diverse function/s of cyclin-dependent kinases not only within the regulation of transcription during development and cellular differentiation, but also in the context of cellular physiology, such as response to given extracellular stimulus, cell response to physiological and stress induced conditions in order to develop new ways how to counteract tumor growth and invasiveness.

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