New therapeutic strategy for chemotherapy resistance in ovarian cancer

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Dr. Rugang Zhang. Credit: The Wistar Institute

A study from The Wistar Institute demonstrated that NAMPT, an enzyme critical for NAD+ biosynthesis, mediates selection of stem-like chemoresistant cells following cisplatin treatment. Researchers showed that a combination of cisplatin treatment with pharmacological inhibition of NAMPT suppresses the outgrowth of resistant cancer cells in vitro and prolongs survival in a preclinical model. These findings were published online in *Cancer Research*.

Epithelial ovarian cancer is the leading cause of death by gynecologic cancers in the United States, with treatment options still limited to surgery and chemotherapy. Unfortunately, chemoresistance to platinum-based drugs represents a major challenge as most patients ultimately relapse and succumb to the disease.

"Based on previous findings from our laboratory, we have identified a molecule that can be pharmacologically blocked to get rid of resistant cells while preserving the beneficial anticancer power of cisplatin, which still remains the standard of care for this disease," said Rugang Zhang, Ph.D., deputy director of The Wistar Institute Cancer Center, professor and co-program leader of the Gene Expression and Regulation Program, and senior author on the paper.

Platinum-based therapies trigger cellular senescence that is accompanied by the emergence of drug-resistant, more malignant cells. Senescent cells stop dividing suppressing tumor growth, but, at the same time, produce a variety of inflammatory molecules. Collectively known as the senescence-associated secretory phenotype (SASP), these molecules can promote proliferation and survival of neighboring cells, ultimately contributing to tumor progression.

Zhang and colleagues previously showed that the NAMPT enzyme drives the activation of the SASP in ovarian cancer cells and that pharmacological inhibition of NAMPT suppresses the SASP.

Drug-resistant cancer cells also possess stem-like properties including expression of the CD133 surface marker and elevated activity of the aldehyde dehydrogenase (ALDH1) enzyme. Since inhibition of ALDH activity sensitizes cancer cells to chemotherapy, it's been suggested that acquisition of the stem-like phenotype is a key step in the emergence of resistance.

In this new study, the team demonstrated that the NAMPT-regulated SASP mediates therapy-induced emergence of senescence-associated stem-like cancer cells.

Importantly, combining cisplatin treatment with NAMPT inhibitors blocked the expression of stem-like markers, suppressed the outgrowth of chemoresistant stem-like cells in vitro and delayed tumor relapse in vivo, significantly prolonging survival of a mouse model of epithelial ovarian cancer.

"NAMPT blockage removes the tumor-promoting effects of cellular senescence while not interfering

with its tumor-suppressive functions," said Zhang. "Our findings suggest that clinically applicable NAMPT inhibitors may be applied to enhance the therapeutic effect of cisplatin and improve the platinum-based standard of care in epithelial ovarian cancer."

More information: Timothy Nacarelli et al, NAMPT inhibition suppresses cancer stem-like cells associated with therapy-induced senescence in ovarian cancer, *Cancer Research* (2019). DOI: 10.1158/0008-5472.CAN-19-2830

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