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Targeting key cancer stem cell pathways overcomes chemo resistance to platinum therapy

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Chemo resistance to platinum therapy is a major obstacle that needs to be overcome in the treatment of solid tumors, including ovarian cancer patients. The high rates and patterns of therapeutic failure seen in ovarian cancer are consistent with a steady accumulation of drug-resistant cancer stem cells (CSCs). Our studies demonstrate that the Notch signaling pathway and Notch3 in particular are critical for the regulation of CSCs and tumor resistance to platinum. We have shown that Notch3 over expression in tumor cells results in expansion of CSCs and increased platinum chemo resistance. In contrast, γ -secretase inhibitor (GSI), a Notch pathway inhibitor, depletes CSCs and increases tumor sensitivity to platinum. Similarly, a Notch3 siRNA knockdown increases the response to platinum therapy, further demonstrating that modulation of tumor chemo sensitivity by GSI is Notch specific. Most importantly, the cisplatin/GSI combination is the only treatment that effectively eliminates both CSCs and the bulk of tumor cells, indicating that a dual combination targeting both populations is needed for tumor eradication. Both platinum-resistant and platinum-sensitive relapses may benefit from such an approach as clinical data suggest that all relapses after platinum therapy are increasingly platinum resistant. Since this increased sensitivity is only observed in tumors with Notch 3 over expression and activation of the Notch pathway, the use of genetic biomarkers to identify which patients are most likely to benefit from GSI-based therapy is critical. In addition, it is important to identify a Notch-based signature to better assess drug responses in clinical trials. A further challenge to the clinical application of GSIs has been their gastrointestinal toxicity and off-target effects. In an attempt to remedy this issue, inhibitory antibodies have recently been synthesized for all Notch receptors, including Notch 3, and they are currently being tested. This will pave the way for new clinical trials to evaluate the efficacy of more selective and less toxic antibody based therapies in enhancing the response to platinum treatment. The overwhelming potential of Notch-based cancer treatments cannot be ignored. Increasing the use of personalized tumor biomarkers and translating these novel therapies into practice holds great promise for achieving a better prognosis in ovarian cancer.

Biography

Daniela Dinulescu is an Assistant Professor at Harvard Medical School. She received her Ph.D. from Oregon Health and Science University and completed her postdoctoral studies in the field of Cancer Genetics at MIT. Dr. Dinulescu's research interests focus on cancer biology, malignancies of the gonads and reproductive tract, with a special emphasis on ovarian cancer research and endometriosis. Our laboratory is actively investigating the key contribution of cancer stem cells (CSCs) to tumor chemoresistance. Our current studies focus on better understanding the mechanism of Notch signaling in the maintenance of the CSC niche and ovarian tumorigenesis. The aim is to harness the power of nanotechnology to develop improved "homing" technologies for the delivery of therapeutic agents specifically targeting and sensitizing ovarian cancer cells, including CSCs, in a spatio-temporal fashion.

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