Targeting FOXM1 in cancer

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The outcomes for acute myeloid leukemia (AML) have remained abysmally poor for the past 30 years. 20-40% of patients fail to achieve remission with induction chemotherapy and 50 -70% of patients who achieve a complete remission relapse within 3 years. A breakthrough in dissecting out prognostic subgroups came with the discovery of the nucleophosmin (NPM1) mutation in 40%-60% of CN-AML cases. In subsequent analyses it has been shown that AML patients with wild-type FMS-like receptor tyrosine kinase (FLT3), bearing mutated NPM1 (*NPM1*^{mut}) showed improved overall survival (OS) and relapse-free survival (RFS). We proposed that mutated NPM1 (*NPM1*^{mut}) confers this advantage in CN-AML via sequestration of FOXM1 in the cytoplasm where FOXM1 is inactive. We have demonstrated that FOXM1, an oncogenic transcription factor, co-localizes with NPM in AML cells. Mutations in NPM1 resulting in its nuclear export will drive FOXM1 to the cytoplasm where it is inactive as a transcription factor. We have shown a correlation between the expression of nuclear FOXM1 and the outcome for AML patients using primary AML samples. Stable knockdown of FOXM1 in AML KG-1 cell line resulted in increased sensitivity to this chemotherapeutic agent This data suggests that targeting FOXM1 in AML could increase sensitivity to standard chemotherapy. Knockdown of NPM1 in cancer cells led to significant down-regulation of FOXM1 suggesting that NPM/FOXM1 interaction is required for FOXM1 expression. in preliminary experiments we identified two compounds that inhibit NPM/FOXM1 interaction and suppress FOXM1 expression in AML cell lines. These compounds preclude binding of NPM and FOXM1 and modulate the suppression of FOXM1. We found that these compounds suppress FOXM1 in a variety of human cancer cell lines of different origin. Overall, our data validate FOXM1 as important target in human cancer and novel NPM/FOXM1 inhibitors that could be developed for cancer patients.

Speaker Biography

Andrei L Gartel is an Associate Professor in the Department of Medicine at the University of Illinois at Chicago and is the Academic Editor of PLOS ONE. He is the author of 89 peer-reviewed publications that include more than 20 reviews. He has more than 10000 citations and his h-index is 39. His scientific interests include: cancer, cell cycle, protein-protein interactions, regulation of CDK inhibitor p21 and regulation of oncogenic transcription factors FOXM1 and c-Myc. Specifically, his lab is interested in identification of new FOXM1 inhibitors. He received his funding from NIH, DOD and private companies/foundations.

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