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Targeting FOXM1 in colon and liver cancer

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death in the United States. Therefore, development of novel therapeutic strategies for the treatment of CRC is extremely important. FOXM1 overexpressed in the majority of CRC and overexpression of FOXM1 plays a critical role in colorectal cancer. Since the FOXM1 regulatory network is a major predictor of adverse outcomes in human cancers, inactivation of FOXM1 by the FOXM1 inhibitors an attractive treatment strategy. Nucleophosmin (NPM) belongs to the nucleophosmin/nucleoplasmin family of chaperones, which are ubiquitously expressed in mammalian cells. FOXM1 interacts with NPM in human cancer cells including CRC cells and NPM knockdown in human cancer cells led to significant down-regulation of FOXM1. Our data suggest that in human cancer cells NPM interacts with FOXM1 and their interaction is required for sustaining the level and localization of FOXM1. We identified two compounds that inhibit NPM/FOXM1 interaction and suppress FOXM1 expression in CRC cell lines. In addition, these compounds synergize with 5-FU in HCT116 CRC cells. NPM consists of pentamers that dimerize into a decamer. The compounds are predicted to bind at two sites on NPM homo-oligomerization domain and they would likely block NPM oligomerization. Therefore, by disrupting monomer-monomer interactions, they are also precluding binding of NPM and FOXM1. We hypothesize that since FOXM1 contributes to the progression and metastasis of CRC, targeting FOXM1 with small molecules will improve treatment outcomes for CRC patients.

Biography

Andrei L Gartel, PhD, 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-review publications that include more than 20 reviews. He has more than 10,000 citations and his h-index is 40. 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 the identification of new FOXM1 inhibitors. He received his funding from NIH, DOD and private companies/foundations.

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