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Targeting FOXM1 in cancer

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FOXM1 is an oncogenic transcription factor that is overexpressed in majority of human cancers and it is a potential target for anticancer drugs. We identified proteasome inhibitors as the first type of drugs that target FOXM1 in cancer cells. Moreover, we found that HSP90 inhibitor PF-4942847 that does not act as proteasome inhibitor also suppresses FOXM1. Chaperone HSP70 is induced after treatment with both proteasome/HSP90 inhibitors and after heat-shock stress and we identified this chaperone as a novel negative regulator of FOXM1 after proteotoxic stress. We showed that FOXM1 and HSP70 interact in cancer cells following proteotoxic stress and FOXM1/HSP70 interaction led to inhibition of FOXM1 binding to target gene promoters, including its own (auto-regulation loop). Inhibition of FOXM1 transcriptional auto-regulation by HSP70 leads to suppression of FOXM1 protein expression because of its auto-regulation. Therefore, we propose here that HSP70 is the universal negative regulator of FOXM1 after proteotoxic stress. In contrast, HSP70 inhibition increased FOXM1 expression and simultaneous inhibition of FOXM1, and HSP70 dramatically augmented the sensitivity of human cancer cells to apoptosis induced by different anticancer drugs. Our study advocates exploring the combination of FOXM1 and HSP70 inhibitors as potential therapeutics for cancer treatment. Overall, our results suggest that HSP70 chaperone induced by proteotoxic stress inhibits FOXM1 oncogene by previously unknown mechanism.

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 86 peer-review publications that include more than 20 reviews. He has more than 8500 citations and his h-index is 36. 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.