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Opposite effects of FOXM1 interactions with partner proteins on its stability and expression

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The oncogenic transcription factor FOXM1 is an attractive therapeutic target in the fight against cancer, because it is overexpressed in a majority of human tumors, while its expression is usually halted in normal non-proliferating cells. Using co-immunoprecipitation and glutathione S-transferase pull-down experiments we demonstrated that NPM forms a complex with FOXM1 and we also identified the regions responsible for their interaction. Furthermore, knockdown of NPM in immortal and cancer cells led to significant down-regulation of FOXM1 similar to its levels in normal cells, suggesting that NPM might modulate FOXM1 level. Our data suggest that in cancer cells NPM interacts with FOXM1 and their interaction is required for sustaining the level and localization of FOXM1. We identified thiazole antibiotics Siomycin A and thiostrepton inhibit transcriptional activity of FOXM1, downregulate FOXM1 protein and mRNA levels and act as proteasome inhibitors. We also found that negative regulation of FOXM1 and up-regulation of HSP70 by proteasome inhibitors are general features of these drugs. In addition, we showed that the HSP90 inhibitor PF-4942847 also efficiently inhibited FOXM1 transcriptional activity and expression. Using immunoblot analysis we found that inhibition of HSP90 also led to induction of HSP70 (could be a marker of activity of this drug) and to down-regulation of FOXM1 protein. Using HSP70 inhibitors we found that suppression of HSP70 led to up-regulation of FOXM1 after treatment by proteasome inhibitors. In addition we found that HSP70 interacts with FOXM1. These data suggest that negative regulation of FOXM1 by proteasome/HSP90 inhibitors is modulated by HSP70.

Biography

Andrei L. Gartel (Ph.D.) is an Associate Professor in the Department of Medicine at the University of Illinois at Chicago, and the academic editor of PLOS ONE. He is the author of 80 peer-review publications that include more than 15 reviews with more than 3000 citations. His scientific interests include cancer, cell cycle, CDK inhibitors, oncogenic transcription factors FOXM1 and c-Myc, and mechanisms of action of anticancer drugs. Recently his lab discovered that FOXM1, which is strongly overexpressed in a human cancer, is a novel major target for proteasome inhibitors. He received his funding from NIH, DOD and private companies/foundations.

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