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The oncogenic transcription factor FOXM1 and anticancer therapy

Andrei L. Gartel

Department of Medicine; University of Illinois at Chicago; Chicago, IL USA

The transcription factor forkhead box M1 (FOXM1) is a member of the forkhead family, and it induces the expression of genes involved in the execution of mitosis. FOXM1 is overexpressed in a majority of human tumors and is implicated in tumor angiogenesis, invasion and metastasis. Increased FOXM1 expression in tumors is associated with late-tumor stage and poor prognosis. These data imply that FOXM1 contributes to oncogenesis, and that cancer cells are dependent on FOXM1. Therefore, targeting FOXM1, the potential Achilles' heel of cancer,[1] alone or in combination with other drugs, is a sound strategy to eliminate tumor cells. However, FOXM1 is a transcription factor that belongs to the group of traditionally undruggable molecules, and it is not easily targeted by traditional drug development approaches. Therefore, therapeutic potential of FOXM1 inhibitors for cancer patients has not been yet explored. To examine the possibility of suppressing FOXM1 in tumors in vivo by siRNA, we encapsulated FOXM1-siRNA into PEI-based nanoparticles and delivered it into xenograft tumors.[2] We found that expression levels of FOXM1 and its transcriptional targets Cdc25B and Aurora B kinase were decreased, while p27, an indirect target of FOXM1 (via suppression of Skp2), was increased in tumors treated with FOXM1-siRNA.[2] Our data suggest that intratumoral delivery of JetPEI-encapsulated FOXM1-siRNA is functional, because it inhibits expression of FOXM1 and its direct targets. FOXM1-siRNA may be effective in vivo and may be used as a proof of principle for the development of new anticancer strategies with FOXM1 inhibitors.

Using screening of chemical libraries, we originally discovered the first FOXM1 inhibitors thiazole antibiotics, Siomycin A[3] and later thiostrepton.[4] Both of these drugs inhibit transcriptional activity and expression of FOXM1[3,4] and act as proteasome inhibitors (PIs).[5] We encapsulated thiostrepton into micelles assembled from amphiphilic lipid-polyethylene glycol, where hydrophobic thiostrepton molecules are solubilized into the lipid component of the micelle shell.[6] We showed that micelle-thiostrepton inhibited growth of human cancer xenografts and suppressed FOXM1 expression in tumors.[6] We demonstrated previously that FOXM1 binds to its own promoter and induces its own transcription and protein expression (auto-regulation loop).[7] Moreover, we established that all PIs that we examined, including bortezomib, MG132, MG115 and others, suppress FOXM1 similarly to thiostrepton and Siomycin A.[5] We proposed a general model of FOXM1 inhibition by PIs:[8] PIs inhibit proteasomal degradation of a negative regulator of FOXM1 (NRFM), which hinders the activity of FOXM1 as a transcription factor. This model predicts that all PIs will inhibit FOXM1 auto-regulation and FOXM1 expression through the stabilization of NRFM.[8] However, since PIs affect not only FOXM1, but also many other cellular functions, more specific FOXM1 inhibitors are needed.

Nucleophosmin (NPM) belongs to the nucleophosmin/nucleoplasmin family of chaperones, which are ubiquitously expressed in mammalian cells. Like FOXM1, NPM is overexpressed in many human carcinomas. We found that FOXM1 interacts with NPM, and NPM knockdown in cancer cells led to significant downregulation of FOXM1. Our data suggest that NPM interacts with FOXM1, and that their interaction is required for sustaining the level and localization of FOXM1.[9] We plan to identify NPM peptides and small molecules that inhibit the interaction between NPM and FOXM1, leading to the destabilization of FOXM1. These peptides and small molecules will act as FOXM1 inhibitors and represent a novel type of drugs against cancer. There are indications that FOXM1 might inhibit apoptosis induced by various anticancer drugs. We have shown that p53 negatively regulates FOXM1,[10] and that following DNA damage, FOXM1 protein levels are often elevated in cancer cells with mutant p53.[11] We demonstrated that combination treatment of human cancer cell lines with FOXM1 inhibitors and DNA-damaging agents led to downregulation of FOXM1 and potent apoptosis.[11] These data suggest that FOXM1 inhibitors may be useful tools for combinatorial treatment of cancer patients. We expect that in the coming years, novel FOXM1 inhibitors will be developed and successfully used against human malignancies.

Correspondence to: Andrei L. Gartel; Email: agartel@uic.edu
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