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Targeting FoxM1 against human cancer

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The oncogenic transcription factor FoxM1 is an attractive therapeutic target in the fight against cancer, because it is over expressed in a majority of human tumors, while its expression is usually halted in normal non-proliferating cells. We identified thiazole antibiotics Siomycin A and thiostrepton as specific inhibitors of FoxM1 transcriptional activity. In addition, we demonstrated that thiostrepton and Siomycin A down regulate FoxM1 protein and mRNA levels. This result was explained by the fact that FoxM1 induces its own expression and by repressing FoxM1 transcriptional activity thiazole antibiotics also inhibit FoxM1 expression. Paradoxically, Siomycin A and thiostrepton stabilize the expression of a variety of proteins, such as p21, Mcl-1, p53 and hdm-2 and also act as proteasome inhibitors in vitro.

We also found that well-known proteasome inhibitors such as PSI, MG132 and Velcade inhibit FoxM1 transcriptional activity and FoxM1 expression. The thiazole antibiotics and proteasome inhibitors induce apoptosis in human cancer cell lines of different origin. Apoptosis induced by thiazole antibiotics and other proteasome inhibitors in human cancer cells correlated with suppression of FoxM1 expression. Interestingly, thiostrepton synergistically induced apoptosis in human cancer cells following combination treatment with proteasome inhibitor bortezomib.

These data suggest that negative regulation of FoxM1 by proteasome inhibitors is a general feature of these drugs and it may contribute to their anticancer properties. In addition, our findings indicate that FOXM1 down regulation by stable or transient knockdown using RNAi or by treatment with proteasome inhibitors that target FOXM1 strongly sensitized human cancer cells of different origin to DNA-damage- or oxidative stress-induced apoptosis. We explored the potential in vivo anticancer properties of thiostrepton, delivered through nanoparticle encapsulation to xenograft models of breast and liver cancer. We encapsulated thiostrepton into micelles assembled from amphiphilic lipid-PEG (polyethylene glycol) molecules, where thiostrepton is solubilized within the inner lipid compartment of the micelle. Upon assembly, hydrophobic thiostrepton molecules are solubilized into the lipid component of the micelle shell, formed through the self-assembly of amphipilic lipid-PEG molecules. Maximum accumulation of micelle-thiostrepton nanoparticles (100nm in diameter,-16mV in zetapotential) into tumors was found at 4 hours post-administration and was retained for at least 24 hours. Upon continuous treatment, we found that nanoparticle-encapsulated thiostrepton reduced tumor growth rates of MDA-MB-231 and HepG2 cancer xenografts. Furthermore, we show for the first time the in vivo suppression of the oncogenic FOXM1 af! ter treatment with thiostrepton.

Immunoblotting and immunohistochemical staining also showed increased apoptosis in the treated tumors, as indicated by cleaved caspase-3 expression. Our data suggest that the thiazole antibiotic/proteasome inhibitor thiostrepton, when formulated into nanoparticles, may be highly suited as a nanomedicine for treating human cancer. Using mass spectrometric analysis we found that oncogenic transcription factor FOXM1 that is over-expressed in a majority of human cancers interacts with multifunctional protein NPM, which is also over-expressed in a variety of human tumors. Coimmunoprecipitation and glutathione S-transferase pull-down experiments demonstrated that NPM forms a complex with FOXM1 and also identified the regions responsible for their interaction. Immunofluorecence microscopy confirmed the interaction between FOXM1 and NPM in cancer and immortal cells. Furthermore, knockdown of NPM in immortal and cancer cells led to significant down-regulation of FOXM1 suggesting that NPM might modulate FOXM1 level. In addition, in OCI/AML3 leukemia cells where mutant NPM is localized in the cytoplasm we found that typically nuclear FOXM1 was predominantly co-localized with NPM in the cytoplasm, suggesting that NPM may determine intracellular localization of FOXM1. Knockdown of FOXM1 or NPM in MIA PaCa-2 ! pancreatic cancer cells inhibited anchorage-dependent and independent growth in cell culture, and tumor growth in nude mice. Our data suggest that in cancer cells NPM interacts with FOXM1 and their interaction is required for sustaining the level and localization of FOXM1. Targeting the interaction between FOXM1 and NPM by peptides or small molecules may represent a novel therapeutic strategy against cancer

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