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Micelle-encapsulated Thiostrepton is an effective nanomedicine for inhibiting tumor growth

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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. We identified thiazole antibiotics Siomycin A and thiostrepton as inhibitors of FoxM1 transcriptional activity. In addition, we demonstrated that thiostrepton and Siomycin A downregulate 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. 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 zeta-potential) 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 after 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 nanomedicinefor treating human cancer. Furthermore, we found that combination of thiostrepton in nanoparticles and bortezomib reduced tumor growth rates more efficiently than compared with when administered alone in xenograft and DEN-PB models of human cancer. Increased induction of apoptotic activity in tumors was found be associated with the growth inhibitory activity of combination treatment. Further examination additionally revealed that combination-treated tumors exhibited reduced proteasome activity, compared with non-treated and single drug-treated tumors. These data suggest that this drug combination may be useful as a therapy for solid tumors.

Biography

Andrei L Gartel, Ph.D. is an Associate Professor in the Departments of Medicine and Biochemistry & Molecular Genetics at the University of Illinois at Chicago. He is the author of more than 75 peer-review publications that include more than 15 reviews with more than 3000 citations. His scientific interests include the cancer, regulation of cell cycle, cyclin dependent kinase inhibitors, oncogenic transcription factors FOXM1 and c-Myc, and mechanisms of action of anticancer drugs. Recently his lab identified oncogenic transcription factor FOXM1, which is strongly overexpressed in a human cancer, as a novel major target for proteasome inhibitors. He received his funding from NIH, DOD and private companies/foundations. He is an academic editor of PLOS ONE.

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