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FOXM1: The Achilles' heel of cancer?

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We read with great interest the Review article by Myatt and Lam (Myatt, S. S. & Lam, E. W. The emerging roles of forkhead box (Fox) proteins in cancer. *Nature Rev. Cancer* **7**, 847–859)[1]. The authors discuss our recent work on the identification of the thiazole antibiotic siomycin A as an inhibitor of FOXM1 function[2]. However, they incorrectly state that siomycin A induces "apoptosis in FOXM1-transformed cells, but not in U2OS osteosarcoma cells of the same origin." In that particular experiment, our attempt was to compare the effect of siomycin A on wild-type and SV40-transformed human fetal lung fibroblasts (MRC-5), and we found that the transformed cells were much more susceptible to apoptosis than their wild-type counterparts. Also we did not claim that the cells were transformed with FOXM1, nor did we try that experiment on U2OS osteosarcoma cells.

Also, the authors make a conclusion that FOXM1 is unlikely to be a direct target of siomycin A[1] on the basis of our observation that this antibiotic antagonizes transcriptional activity as well as mRNA and protein levels of FOXM1 (REF. 2.) However, the evidence presented in our study, in concert with our recent experiments, paints a different picture. First, we showed that overexpression of exogenous FOXM1 led to an increase in the endogenous FOXM1 protein levels[2]. Second, we demonstrated that siomycin A treatment decreased the endogenous FOXM1 protein and mRNA, but not the exogenous FOXM1 protein levels[2]. Based on these observations we propose that FOXM1 might be involved in a positive feedback loop. If this loop is necessary for FOXM1 expression, then just by blocking the transcriptional activity of FOXM1 siomycin A could elicit a decrease in its mRNA and protein levels. In fact, our recent experiments, in which we saw an increase in mRNA levels of endogenous FOXM1 upon overexpression of exogenous FOXM1 (M. Halasi, U. G. Bhat and A.L.G., unpublished observations), seem to support this notion.

Mechanism aside, FOXM1 appears to be an attractive therapeutic target in cancer[3]. Whereas FOXM1 expression is extinguished in terminally differentiated cells, it has been found to be upregulated and/or required in a number of different cancers, including basal cell carcinoma, hepatocellular carcinoma, glioblastoma, primary breast cancer, lung cancer and prostate cancer[4–9]. This over-reliance of cancer cells on FOXM1 is a fatal weakness that could be exploited in the clinic for devising therapeutics with minimal side effects. What is more exciting is the accumulating evidence that implicates FOXM1 in other related processes such as tumour invasion, angiogenesis and metastasis[10–12]. Thus, by inhibiting this single transcription factor, it should be possible to target multiple facets of tumorigenesis.

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