Abstract for Student Research Conference
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Is FoxM1 the Therapeutic Target of Thiostrepton in Malignant Mesothelioma?

Malignant mesothelioma (MM) is a highly aggressive cancer of the lung which arises as a solid, invasive, destructive tumor and is often associated with asbestos exposure. With no effective treatment available, most patients die within 18 months of diagnosis, though the cancer may remain latent for more than 50 years. FoxM1, a transcription factor critical in the regulation of the cell cycle, has been linked to carcinogenesis. FoxM1 is not expressed in quiescent cells and is over-expressed in many highly proliferative cancers such as MM. Many studies suggest that FoxM1 is a potential target for anti-cancer therapies.

A previous small molecule screen on FoxM1 detected a thiopeptide antibiotic called thiostrepton. Thiostrepton has been shown to inhibit FoxM1 transcription and expression, inhibit cell growth and induce cell death in human cancer cell lines. A prior study showed that FoxM1 and thiostrepton interact directly. Based upon this interaction, our hypothesis is that FoxM1 is critical for the cytotoxic activity of thiostrepton. If the target of thiostrepton is FoxM1, depletion of FoxM1 from MM cells should limit the cytotoxic activity of thiostrepton.

Results of FLOW cytometry and colony formation assays, however, show the cytotoxic activity of thiostrepton is not inhibited by the depletion of FoxM1. This demonstrates that FoxM1 is not critical for the cytotoxic activity of thiostrepton. Although FoxM1 expression is influenced by thiostrepton, as demonstrated in previous studies, FoxM1 is not the only intracellular target of thiostrepton.

FoxM1 was depleted from normal mesothelial cells and MM cells through siRNA-knockdown specific of the FoxM1 mRNA. The cells were subsequently treated with thiostrepton in varying concentrations. FLOW cytometry analyzed cell-cycle progression, cell viability was measured through colony formation assay using crystal violet, and si-RNA knockdown of FoxM1 was characterized through immunoblotting and qRT-PCR mRNA analysis.