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The role of FOXM1 in cancer

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FOXM1 is overexpressed in the majority of human cancers and its expression correlates with unfavorable prognosis. Since the FOXM1 regulatory network is a major predictor of adverse outcomes in human cancers, inactivation of FOXM1 by the FOXM1 inhibitors an attractive treatment strategy. Nucleophosmin (NPM) belongs to the nucleophosmin/nucleoplasmin family of chaperones, which are ubiquitously expressed in mammalian cells. FOXM1 interacts with NPM in human cancer cells and NPM knockdown in human cancer cells led to significant down-regulation of FOXM1. Our data suggest that in human cancer cells NPM interacts with FOXM1 and their interaction is required for sustaining the level and localization of FOXM1. In some cases of AML mutant NPM re-localizes to the cytoplasm. We found that improved outcome for AML patients with mutant NPM1 is linked to the cytoplasmic localization and consequent functional inactivation of FOXM1 that driven by mutant NPM to the cytoplasm. This premise suggests that nuclear FOXM1 is one of the drivers for AML development. We identified two compounds that inhibit NPM/FOXM1 interaction and suppress FOXM1 expression in human cancer cell lines. In addition, these compounds synergize with different chemotherapeutic drugs. The compounds are predicted to bind at two sites on NPM homo-oligomerization domain and they would likely block NPM oligomerization. Therefore, by disrupting monomer-monomer interactions, they are also precluding binding of NPM and FOXM1. We hypothesize that since FOXM1 contributes to the progression and metastasis of human cancer, targeting FOXM1 with small molecules will improve treatment outcomes for cancer patients.

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