STRONG CHILDREN'S RESEARCH CENTER

Summer 2018 Research Scholar

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ABSTRACT

Title: *Targeting the HE4-Sept2 interaction to develop novel drugs for gynecologic cancers*

Background: Human epididymis protein 4 (HE4) is a secreted protein that may be implicated in various biological functions relating to cancer. Recent co-immunoprecipitation and mass spectroscopy analyses indicate that Septin 2 (Sept2), a cytoskeletal GTP-binding protein, interacts with HE4. Septins are also involved in cell proliferation, angiogenesis, and resistance to microtubule-targeting chemotherapy. Findings suggest that high Sept2 expression correlates with low survival rates among patients with endometrial cancer. Additionally, HE4 is a useful clinical biomarker for ovarian cancer because it is overexpressed by epithelial ovarian cancer cells.

Objective: The HE4-Sept2 interaction necessitates further understanding in the context of cancer treatment.

Results: Here, we analyze the cytotoxicity of seven newly-synthesized compounds that affect HE4 and Sept2 expression levels on various gynecologic cancer cell lines. These drugs are novel, small-molecule inhibitors of septins. Two of these drugs (Compound 1 and Compound 7) diminish secreted HE4 expression levels, in addition to reducing cell viability, more efficiently than a known-Septin inhibitor called forchlorfenuron (FCF). Since Compound 7 is significantly more potent than FCF, we derived and synthesized four new analogs of Compound 7 to optimize drug potency (Compound 7A, Compound 7B, Compound 7C, and Compound 7D). All four novel compounds exhibit profound cytotoxicity on various ovarian and endometrial cancer cells.

Conclusion: Our results corroborate the significance of the HE4-Sept2 interaction in ovarian and endometrial cancers and motivate the manipulation of these proteins for potential cancer therapies.