Poster 42: Chemical inhibition of SWI/SNF induces transformed growth in non-mutant cells, mimicking the effects of a SMARCA4 mutation associated with small cell carcinoma of the ovary, hypercalcemic type.

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Topic: Ovarian

Objectives

Using a chemical inhibitor of the SWI/SNF complex (BRM014), we sought to determine if non-cancerous cells harboring wild-type SMARCA4 would spontaneously transform during in vitro culture, thereby providing a new model system for studying the formation of SCCOHT.

Methods

Ovarian cells derived from a benign ovarian cyst removal (P583) were serially passaged in media containing BRM014, an inhibitor of the ATPase domains of SMARCA4 and SMARCA2. Cells were interrogated for their ability to acquire characteristics of cellular transformation. Cells were grown for multiple passages to determine if cells would spontaneously immortalize. Loss of contact-dependent inhibition was interrogated with focus-forming assays of confluent monolayers. The ability of cells to escape anoikis and grow independently as spheroids was interrogated in attachment-free growth conditions. All experiments were compared to experiments conducted with an age-matched cell population derived from a familial carrier of a SCCOHT-associated mutation in the SMARCA4 gene (P590, SMARCA4. c.3081+1G>T, prophylactic oophorectomy).

Results

P583 cells that were treated with BRM014 formed markedly larger spheroids in attachment-free conditions compared to vehicle control-treated cells. BRM014-treated cells also formed foci in confluent monolayers, while none formed in vehicle control-treated cells. These results phenocopied the growth properties of P590 cells, indicating that inhibition of SMARCA4 and SMARCA2 could mimic the effects of SMARCA4 mutation. Of particular interest was the persistence of treatment: After as little as 48 hours of treatment, cells retained the ability to grow as spheroids for at least 7 days following removal of BRM014.

Conclusions

Through the use of a chemical inhibitor of SMARCA4 and SMARCA2, non-mutant ovarian cells were induced to grow in a manner consistent with early stages of transformation, similar to cells harboring a SMARCA4 mutation associated with familial SCCOHT. Our data suggest that through the use of BRM014, multiple pseudo-transformed cell populations can be formed from diverse, non-mutant patient samples, providing robust cellular tool for studying the early stages of SCCOHT formation.