A novel compound ARN-3236 inhibits SIK2 and sensitizes ovarian cancer to paclitaxel

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Abstract

Ovarian carcinomas account for 4% of all cancers in women in the United States. Taxanes are microtubule-stabilizing agents commonly used in several solid tumors, including ovarian cancer. However, only a fraction of patients will benefit because inherent or acquired resistance confounds the effective treatment of ovarian cancer. Improved outcomes might be attained if sensitivity to primary chemotherapy were enhanced. There is an unmet need to discover new therapeutic strategies that may improve ovarian cancer response to taxane-based chemotherapy. A recent study discovered that the salt inducible kinase 2 (SIK2) plays a key role in mitosis progression and regulates paclitaxel sensitivity in ovarian cancer. Here we show that SIK2 is upregulated in 30% of serious ovarian cancer specimens, which underlines the clinical importance of treating ovarian cancer by blocking SIK2 kinase activity. ARN-3236, a selective, highly potent, orally available small molecule SIK2 inhibitor with function similar to SIK2 siRNA, blocks cell proliferation in a panel of 10 ovarian cancer cell lines where the IC50 ranges from 0.8 μM to 2.6 μM. Moreover importantly, the IC50 of ARN-3236 was inversely correlated with endogenous SIK2 expression in ovarian cancer cell lines. ARN-3236 also enhanced response to paclitaxel in cultured ovarian cancer cells which showed detectable SIK2 expression by western blot (OC316, OVCAR6, OVCAR8, A2780, OVCAR5, HEY, ES2 and UPN251) as well as in vivo xenograft models. Similar to the function of SIK2 siRNA, ARN-3236 uncouples the centrosome from the nucleus in interphase, blocks centrosome separation in mitosis, resulting in the accumulation of cells in prometaphase. ARN-3236 also shows induction of G2/M cell cycle arrest, cell apoptosis, and cell polyplody. RPPA analysis after ARN-3236 treatment identified p-AKT as the top hit of downregulated signaling pathways, which was confirmed by western blot. ARN-3236 effectively inhibits AKT phosphorylation at Ser473 and Tyr308, as well as the expression of the downstream effector survivin. Cell sublines which were engineered to express survivin decreases paclitaxel sensitization and apoptosis induction by ARN-3236. Based on above results, ARN-3236 may significantly improve the sensitivity of paclitaxel for treatment of human ovarian cancers.

Results

SIK2 is overexpressed in serous ovarian cancer

ARN-3236 inhibits SIK2 activity and cell growth

ARN-3236 uncouples centrosome from nucleus and blocks centrosome splitting

ARN-3236 sensitizes ovarian cancer to paclitaxel

Conclusions

SIK2 is overexpressed in serous ovarian cancer specimens. ARN-3236 selectively inhibits SIK2 kinase activity and blocks ovarian cancer cell growth.

ARN-3236 sensitizes ovarian cancer cells to paclitaxel.

ARN-3236 induces prometaphase arrest by inhibiting centrosome splitting in mitotic cells. ARN-3236 leads to cell G2/M arrest, cell apoptosis, and cell polyplody.

ARN-3236 inhibits AKT/survivin pathway.

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