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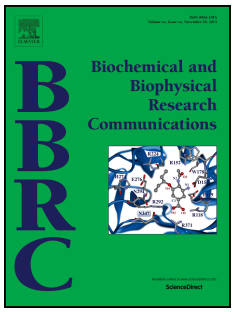

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SMIFH2-mediated functional mDia formin inhibition potentiates chemotherapeutic targeting of human ovarian cancer spheroids

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ABSTRACT

Due to a lack of effective screening or prevention protocol for epithelial ovarian cancer (EOC), there is a critical unmet need to develop therapeutic interventions for EOC treatment. EOC metastasis is unique. Initial dissemination is not primarily hematogenous, yet is facilitated through shedding of primary tumor cells into the peritoneal fluid and accumulating ascites. Increasingly, isolated patient spheroids point to a clinical role for spheroids in EOC metastasis. EOC spheroids are highly invasive structures that disseminate upon peritoneal mesothelium, and visceral tissues including liver and omentum. Selection for this subset of chemoresistant EOC cells could influence disease progression and/or recurrence. Thus, targeting spheroid integrity/structure may improve the chemotherapeutic responsiveness of EOC. We discovered a critical role for mammalian Diaphanous (mDia)-related formin-2 in maintaining EOC spheroid structure. Both mDia2 and the related mDia1 regulate F-actin networks critical to maintain cell-cell contacts and the integrity of multi-cellular epithelial sheets. We investigated if mDia2 functional inhibition via a small molecule inhibitor SMIFH2 combined with chemotherapeutics such as taxol and cisplatin to inhibit the viability of EOC monolayers and clinically relevant spheroids. SMIFH2-mediated mDia formin inhibition significantly reduced both ES2 and Skov3 EOC monolayer viability while spheroid viability was minimally impacted only at the highest concentrations. Combining either cisplatin or taxol with SMIFH2 did not significantly enhance the effects of either drug alone in ES2 monolayers, while Skov3 monolayers treated with taxol or cisplatin and SMIFH2 showed significant additive inhibition of viability. ES2 spheroids were highly responsive with clear additive anti-viability effects with dual taxol or cisplatin with SMIFH2 treatments. While combined taxol with SMIFH2 in spheroids showed an additive effect relative to single treatments, Skov3 spheroids showed no additive effects from combined cisplatin and SMIFH2 treatments. Our data indicate that mDia formin inhibition combined with taxol to drive enhanced and/or additive anti-viability effects targeting 3D EOC structures, including ES2 and Skov3 spheroids. Combined mDia formin inhibition with cisplatin may be most effective in EOC spheroids where cisplatin sensitivity is retained at moderate levels, such as ES2.

KEYWORDS – cytoskeleton; ovarian cancer; formin, spheroid; mDia; SMIFH2

ABBREVIATIONS

EOC – epithelial ovarian cancer
mDia – mammalian Diaphanous-related formin