Manzamine-A targets androgen receptor signaling and synergizes with cisplatin to kill prostate cancer cells

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Background: Androgen receptor (AR) plays a vital role in the development and progression of prostate cancer metastasis, and androgen deprivation therapy (ADT) remains a fundamental clinical treatment for the metastatic stage of this disease. However, the progression of the disease resistant to ADT leads to castration-resistant prostate cancer, along with the development of new AR variants (AR-V7).

Methods: Manzamine-A (MA) is a natural product from the marine sponge and has shown its biological effects in several cancer types. This study demonstrates the antiproliferative and proapoptotic effect of MA in both androgen-responsive (LNCaP and 22Rv1) and androgen-resistant (PC3 and DU145) prostate cancer cell lines.

Results: We demonstrated that the MA significantly inhibited the growth of the tested cell lines in a dose- and time-dependent manner, as evidenced by the cell viability, cell proliferation, and colony formation assays. MA blocked the cell cycle and their regulating proteins CDK4, CDK6, Cyclin D1, and p21. The proapoptotic activity of MA was exerted following PARP cleavage and caspase-3 activation in LNCaP, 22Rv1, and DU145 cells. Interestingly, MA downregulates the AR protein and its downstream target PSA, and AR variant (AR-V7). Examination of molecular signaling revealed that the MA differentially regulates expression levels of total AKT, GSK-3β, pAKT, and pGSK3β proteins in androgen-responsive and -resistant prostate cancer cell lines. Finally, MA sensitizes prostate cancer cells for an effective killing by the chemotherapy drug cisplatin.

Conclusions: The differential activity of MA against androgen-responsive LNCaP and 22Rv1, and androgen-resistant PC3 and DU145 prostate cancer cells suggests a novel mechanism of marine natural product MA targeting cancer cells at different stages of tumor progression. The molecular mechanism and the therapeutic potency of MA as a single agent or in combination with chemotherapy drugs targeting prostate cancer will be determined in future studies.