A NOVEL NEUTRALIZING ANTIBODY TARGETING PAPP-A INHIBITS TUMOR GROWTH AND ASCITES IN PRIMARY PATIENT OVARIAN TUMORGRAFTS (OVATARS)

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The majority of ovarian cancer patients acquire resistance to standard platinum chemotherapy and novel therapies to reduce tumor burden and ascites accumulation are needed. Pregnancy-associated plasma protein-A (PAPP-A) plays a key role in promoting insulin-like growth factor (IGF) pathway activity, which directly correlates to ovarian cancer cell transformation, growth and invasiveness. Herein, we evaluate PAPP-A expression in tumors and ascites of women with ovarian cancer, and determine the anti-tumor efficacy of a neutralizing monoclonal PAPP-A antibody (mAb-PA) in ovarian cancer using primary patient ovarian tumorgrafts (“Ovatars”). PAPP-A mRNA expression in patient ovarian tumors correlated with poor outcome and was validated as a prognostic surrogate in Ovatar tumors. Following confirmation of mAb-PA bioavailability and target efficacy in vivo, the anti-tumor efficacy of mAb-PA in multiple Ovatar tumor models was examined and the response was found to depend on PAPP-A expression. Strikingly, the addition of mAb-PA to standard platinum chemotherapy effectively sensitized platinum-resistant Ovatar tumors. PAPP-A protein in ascites was also assessed in a large cohort of patients and very high levels were evident across the entire sample set. Therefore, we evaluated targeted PAPP-A inhibition as a novel approach to managing ovarian ascites, and found that mAb-PA inhibited the development, attenuated the progression and induced the regression of Ovatar ascites. Together, these data indicate PAPP-A as a potential palliative and adjunct therapeutic target for women with ovarian cancer.