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Targeting Tissue Transglutaminase for Preventing Ovarian Cancer Dissemination †

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Abstract: Tissue transglutaminase (TG2) is a multifunctional protein overexpressed in many solid cancers, including ovarian cancer (OC). In OC, TG2 enables intraperitoneal disease dissemination and metastasis through various mechanisms, including its interaction with fibronectin (FN). This protein-protein interaction (PPI) stabilizes the complex between FN and integrin, thereby increasing cell adhesion to the extracellular matrix. Also, we have shown in mice that loss of TG2 in the host decreases tumor burden, concomitantly with an enhanced anti-tumor immune response (*Sima LE et al., JITC 2021*). This supports the hypothesis that TG2 is a promising therapeutic target for OC treatment. Several small molecule inhibitors (SMIs) were identified during an initial high throughput screening that interferes with TG2-FN PPI. Based on the structure-activity relationship, new compounds were synthesized (MT1-6), out of which MT4 showed the best solubility and inhibitory activity (*Sima LE et al., Mol Cancer Ther 2019*). We are continuing the lead optimization by testing the action of new analogs (#2997, #2998, #3002, #3010, and #3011). Three molecules showed promising effects: i) #2997 decreased SKOV3 cell migration; ii) #3002 inhibited SKOV3 cell adhesion as well as cell cycling, which indicates a potential cytostatic activity; phosphoflow experiments showed an attenuated pFAK signaling in cells treated with #3002; iii) noteworthy, inhibitor #3011 prevented spheroid formation, which makes it extremely promising for the intraperitoneal treatment of OC patients. Our newly developed microfluidic set-up revealed inhibition of mesothelial clearance by SKOV3 spheroids in the presence of MT-4. Further, we detected upregulated sirtuin phosphopeptides by SILAC-based phosphoproteomics as adaptation in attached OC cells under MT-4 treatment. Sirtuins represent a druggable co-target, which would enhance TG2-FN inhibitors efficacy in OC treatment that we currently test *in vitro*.

Keywords: ovarian cancer; tissue transglutaminase; fibronectin; metastasis; small molecule inhibitors.

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Conflicts of Interest

The authors declare no conflict of interest.