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Blocking 17? hydroxysteroid dehydrogenase type 1 in endometrial cancer: a potential novel endocrine therapeutic approach

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Context: Type 1 17?hydroxysteroid dehydrogenase (17?HSD-1), responsible for generating active 17?estradiol (E2) from low-active estrone (E1), is over-expressed in endometrial cancer (EC) thus implicating an increased intra-tissue generation of E2 in this estrogen-dependent condition.
Objective: Explore the possibility to inhibit 17?HSD-1 and impair the generation of E2 from E1 in EC for potential therapeutic purposes. Various in vitro, in vivo and ex vivo models were used.
Methods and Patients: We generated EC cell lines derived from the well-differentiated endometrial adenocarcinoma Ishikawa cells and expressing levels of 17?HSD-1 similar to human tissues (Ishi-HSD1). High-performance-liquid-chromatography (HPLC) was used to measure the 17?HSD-1 activity in cell free assay. Estrogen dependent growth and the ability to inhibit 17?HSD-1 activity were assessed in a colony formation assay and in vivo using the chicken chorioallantoic membrane assay (CAM). Two retrospective EC patient cohorts were used to test inhibition (HPLC) and to determine 17?HSD-1 expression (RT-PCR) in paired primary/metastatic lesions.
Results: Using Ishi-HSD1 cells, E1 to E2 conversion and 17?HSD-1 activity were blocked by a specific 17?HSD-1 inhibitor in cell-free assay followed by HPLC analysis. In vitro, E1 administration elicited colony formation similar to E2, and this was impaired by 17?HSD-1 inhibition. In vivo, tumours grafted on the CAM demonstrated that E1 upregulated the expression of the estrogen responsive cyclin A similar to E2, which was impaired by 17?HSD-1 inhibition. Neither in vitro nor in vivo effects of E1 were observed using 17?HSD-1 negative cells (negative control). Using a patient cohort of 52 primary ECs, we demonstrated the presence of 17?HSD-1 enzyme activity, which was inhibited using the 17?HSD-1 inhibitor by over 90% in more than 45% of ECs. Since drug treatment is generally indicated for metastatic/recurrent and not primary tumour, we next demonstrated the mRNA expression of the potential drug target, 17?HSD-1, in metastatic lesions using a second cohort of 37 EC patients.
Conclusion: 17?HSD-1 inhibition efficiently blocks the generation of E2 from E1 using various EC models. Further preclinical investigations and 17?HSD-1 inhibitor development to make candidate compounds suitable for the first human studies are awaited.

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