Thyroid Hormone Receptors Predict Prognosis in BRCA1 Associated Breast Cancer in Opposing Ways.

Abstract:
Since BRCA1 associated breast cancers are frequently classified as hormone receptor negative or even triple negative, the application of endocrine therapies is rather limited in these patients. Like hormone receptors that bind to estrogen or progesterone, thyroid hormone receptors (TRs) are members of the nuclear hormone receptor superfamily. TRs might be interesting biomarkers - especially in the absence of classical hormone receptors. The current study aimed to investigate whether TRs may be specifically expressed in BRCA1 associated cancer cases and whether they are of prognostic significance in these patients as compared to sporadic breast cancer cases. This study analyzed TR? and TR? immunopositivity in BRCA1 associated (n = 38) and sporadic breast cancer (n = 86). Further, TRs were studied in MCF7 (BRCA1 wildtype) and HCC3153 (BRCA1 mutated) cells. TR? positivity rate was significantly higher in BRCA1 associated as compared to sporadic breast cancers (p = 0.001). The latter observation remained to be significant when cases that had been matched for clinicopathological criteria were compared (p = 0.037). Regarding BRCA1 associated breast cancer cases TR? positivity turned out to be a positive prognostic factor for five-year survival (p = 0.007) and overall survival (p = 0.026) while TR? positivity predicted reduced five-year survival (p = 0.030). Activation of TR? resulted in
down-modulation of CTNNB1 while TR? inhibition reduced cell viability in HCC3153. However, only BRCA1 wildtype MCF7 cells were capable of rapidly degrading TR?1 in response to T3 stimulation. Significantly, this study identified TR? to be up-regulated in BRCA1 associated breast cancer and revealed TRs to be associated with patients’ prognosis. TRs were also found to be expressed in triple negative BRCA1 associated breast cancer. Further studies need to be done in order to evaluate whether TRs may become interesting targets of endocrine therapeutic approaches, especially when tumors are triple-negative.