TOP2A and EZH2 provide early detection of an aggressive prostate cancer subgroup

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Background: Current clinical parameters do not stratify indolent from aggressive prostate cancer (PCa). Aggressive PCa, defined by the progression from localized disease to metastasis, is responsible for the majority of PCa-associated mortality. Recent gene expression profiling has proven successful in predicting the outcome of PCa patients, however they have yet to provide targeted therapy approaches that could inhibit a patient's progression to metastatic disease.

Methods: We have interrogated a total of seven primary PCa cohorts (N = 1,900), two metastatic castration resistant PCa datasets (N = 293) and one prospective cohort (N = 1,385) to assess the impact of *TOP2A* and *EZH2* expression on PCa cellular program and patient outcomes. We also performed immunohistochemical staining for TOP2A and EZH2 in a cohort of primary PCa patients (N = 89) with known outcome. Finally, we explored the therapeutic potential of a combination therapy targeting both TOP2A and EZH2 using novel PCa-derived murine cell lines.

Results: We demonstrate by genome-wide analysis of independent primary and metastatic PCa datasets that concurrent TOP2A and EZH2 mRNA and protein up-regulation selected for a subgroup of primary and metastatic patients with more aggressive disease and notable overlap of genes involved in mitotic regulation. Importantly, TOP2A and EZH2 in PCa cells act as key driving oncogenes, a fact highlighted by sensitivity to combination-targeted therapy.

Conclusions: Overall, our data supports further assessment of TOP2A and EZH2 as biomarkers for early identification of patients with increased metastatic potential that may benefit from adjuvant or neo-adjuvant targeted therapy approaches.

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