Characterization of hormone-sensitive and castrate-resistant phenotypes in prostate cancer patient-derived PDX models generated from the same patient.

Prostate cancer (PCa) is a highly heterogeneous and complex disease, with evolving treatment options over the course of disease progression. Preclinical PCa research is hampered by a lack of predictive models fully capturing all phases of this multistage disease. Despite progresses in the development of genetically-engineered animal models, these ones do not recapitulate faithfully (i) human disease and (ii) tumor heterogeneity. Models obtained by xenografting human tumors in immunodeficient animals (PDX models, for patient-derived tumor xenografts) remain unavoidable tools in PCa translational and preclinical research since they closely conserve cancer characteristics observed in patients. PDX models are thus invaluable tools to evaluate new potential therapeutic agents. We are presenting here the characteristics of two PDX models derived from the same patient before and after acquisition of the hormone-resistance status.

Samples of PCa were obtained from patients at surgery and then subcutaneously xenografted into immunocompromised mice to establish PDX models. After the first growth in mice, they were serially passaged *in vivo*, considering a model established from P3. PDX tumors at multiple passages and patients' primary tumors from which they are derived were processed for further analyses. Specifically, we performed histological, genetic (AR, PTEN, P53 and ERG status), transcriptomic (Affymetrix U133 plus 2.0 microarray) and STR profiles analyses. In addition, we also evaluated the responses of the PDX models to androgen deprivation and docetaxel.

Since 9 years, 252 prostatic tumors have been collected at all stages. Up to now, 7 PDX models were successfully established (> P3 in mice), i.e. 2.7 % success rate. All histological, genetic and molecular analyses validated the stability of the models compared to the parental tumor. Interestingly, we were able to generate one matched pair of responsive and castration resistant models from the same patient. These two PDX models displayed the major molecular features of the disease in humans including PTEN, TP53 and AR modifications. In addition, *in vivo* results show heterogeneity of response to androgen deprivation and docetaxel, similar to the responses of patients to these treatments.

Considering the scarcity of useful PDX models for PCa and the difficulties to develop such models, the PDX models collection presented here should clearly help to open the road of cure for patients with advanced PCa.

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