High specific characterization of patient-derived tumor xenograft models for accelerating drug development in muscle-invasive bladder cancers.

Muscle-invasive bladder cancers (MIBCs) constitute a heterogeneous group of tumors with a poor outcome. Recently, MIBC molecular subtyping efforts from an international consortium led to the identification of six subtypes to improve prediction of clinical outcomes and treatment responses. These subtypes can be schematically divided into luminal (differentiated) and non-luminal subtypes. FGFR3 alterations (mutations and translocations) are among the most frequent genetic events in bladder carcinoma and are found mainly in one subtype, the luminal papillary that respond poorly to chemo- and immuno-therapy. Here we describe the development and characterization of patient-derived primary MIBC xenografts (PDX) belonging to these different subtypes.

Bladder primary tumors and normal corresponding tissues were directly obtained from patients at surgery. Tumor fragments were subcutaneously xenografted into immune-compromised mice. After the first growth in mice, they were serially passaged. PDXs tumors at multiple passages and patients' primary tumors from which they are derived were processed for analyses including growth characteristics, histopathology (H&E, CK5/6, FOXA1 and GATA3), gene expression (Affymetrix U133 plus 2.0 microarray), genetic stability (STR profiling). Specifically, hotspot oncogenic mutations including *FGFR3, PIK3CA, HRAS, KRAS, NRAS, and PPARG* were also explored. Additionally, pharmacological responses to standards of care and targeted therapies were characterized.

Since 10 years, we have collected 152 MIBC tumors at all stages and grades. Up to now, 32 PDX models have been successfully established (> P3 in mice), i.e. 21.1 % success rate. This take rate seems not to be correlated to any classical tumor characteristics. Importantly, transcriptomic analysis allowed us to identify PDX models belonging to the different molecular subtypes including the basal-like and the luminal papillary subtypes (which include several PDX with FGFR3 mutations). All histological, genetic and molecular features validated the stability of the PDX models compared to the parental tumors. Histological analyses were correlated with the molecular classification. These models reproduced the response to cisplatin-based therapies observed in the clinic and FGFR3-mutated PDX models were shown to be highly responder to FGFR3 inhibitors.

We have developed highly relevant preclinical models for MIBCs corresponding to the main subtypes which have been described. They represent essential tools for developing adapted and efficient therapies against this deadly disease.

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