Genomic features of Patient-Derived Xenografts of gastric cancer and transformation to lymphoma during its establishment

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Purpose: The patient-derived xenograft (PDX) model is emerging as a promising translational platform to replicate the characteristics of tumors. However, genomic and molecular characteristics were rarely reported for model fidelity of gastric cancer.

Methods: The histology of established PDX tumors was reviewed and compared to the corresponding primary tumors (F0) by pathologist. To compare the genomic features between F0 and established PDX tumors (F3), whole exome and transcriptome sequencing were conducted with HISEQ 2500 sequencing system (Illumina™) in two representative PDX models (GA006 and GA013).

Results: Fifteen PDX models (F1) were successfully established and sub-passaged in immune-compromised mice (24.2%, 9 from NOG mice and 6 from nude mice) from 62 donor pateints. The histology of PDX tumors was well-matched with those of F0 in 10 out of 15 cases. The genomic features of PDX tumors were similar to F0 in terms of 726 cancer-related genes: all the cancer-related genes were stable, allele frequencies of them and mRNA expression levels of cancer-related genes were well correlated. Histologic changes were detected in five among 15 established PDX models. Immunohistochemistry and *in situ* hybridization revealed that all of them were Epstein-Barr virus (EBV) associated B-cell lymphoma. These unanticipated events seemed to be related to the strain of mouse which was used for establishment of PDX model: all five EBV lymphoma cases were occurred only in NOG strain, and the nude strain showed immunity to this event.

Conclusions: High fidelity in the histological and genomic features of the PDX model compared with the corresponding primary tumor demonstrated that the PDX model can be translated into clinical practice for the development of effective personalized therapeutics for gastric cancer. The risk of transformation to lymphoma should be taken into account when establishing PDX models using highly-immunocompromised mice.