Xenograft-associated B cell lymphoproliferative disease as a surrogate model to study Epstein-Barr Virus (EBV) driven lymphoma of the elderly

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Abstract

Background: Patient-derived tumor xenografts (PDX) are powerful tools to study cancer biology, cancer genomics and developmental therapeutics. A common problem in the development of PDX models is proliferation of atypical lymphocytes at the implant site, which often overtake or limit the growth of the original tumor. This atypical proliferation has been described as Xenograft Associated Lymphoproliferative Disease (XABLD) in our PDX models. In this study, we characterized XABLD cases by morphology, immunophenotyping and genomic profiling. We hypothesize that XABLD tumors are morphologically and phenotypically similar to EBV-driven lymphomas of the elderly and may function as a surrogate model for that lymphoma.

Materials and Methods: Models were generated from patient tissue collected under NCI Tissue Procurement Protocol (https://pdmr.cancer.gov#content#pdmr-nct00900198) and CIRB Tissue Procurement Protocol (https://pdmr.cancer.gov#content#pdmr-nct00900198) for development of models for NCI Patient-Derived Models Repository. Specimens were implanted subcutaneously in NOD/SCID/IL2Rγnull (NSG) mice and animal health was monitored throughout the study. Tumors in mice with suspected XABLD were harvested and reviewed by histology and immunohistochemical analysis. CD4+ T cell and B cell markers and EBV status. All samples in this study were classified by the lymphoid Tumor Cell of Origin assay and transcriptomic profiling.

Results: XABLD-associated mice had rapidly growing CD4+ positive tumors at the implantation site. Morphological features were consistent with EBV-driven diffuse large-B cell lymphoma (DLBCL) primarily of polymorphous subtype. All XABLD specimens were diffusely positive for EBV. In the majority of cases, XABLD tumors were morphologically similar to EBV-driven lymphomas of the elderly.

Conclusion: XABLD tumors are morphologically and phenotypically similar to EBV-driven lymphomas of the elderly. We hypothesize that XABLD tumors may be used as surrogate models for preclinical research.

Some XABLD models have significant T cell involvement

XABLD cases cluster with ABC-subtype DLBCL

XABLD models exhibit elevated NF-kB pathway activity

References


Conclusions

- XABLD are lymphomas originating from B cells present in solid tumors
- XABLD represent EBV positive DLBCL-like tumors
- Characterize mutations and aneuploidy by whole exome sequencing
- XABLD may be useful as surrogate DLBCL models for preclinical research
- XABLD models may have significant T cell involvement
- EBV+ DLBCL are known to have elevated NF-kB signaling
- Single-sample GSEA enrichment scores for 24 NF-kB target genes
- Public EBV- and EBV+: Published DLBCL data

Future work

- Further characterized XABLD for:
  - IGH and IGK B-cell clonality assay
  - EBV latency typing
  - Compare gene expression profile of XABLD to DLBCL
  - Generate XABLD cell line models
  - Compare treatment response of XABLD and DLBCL models

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