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

Some XABLD cases have significant T cell activity

Background: Patient-derived tumor xenografts (PDX) are powerful tools to study cancer biology, cancer genomics and develop candidate therapies. A common problem in the development of PDX models is proliferation of stromal lymphocytes at the implantation site, which often overtakes or limits the growth of the original tumor. This stromal lymphoproliferative process has been described as xenograft associated B cell lymphoproliferative disease (XABLD) in our PDX models. In this study, we characterized XABLD cases by morphology, immunophenotyping and genomic profiling. We hypothesized that XABLD tumors are morphologically and phenotypically similar to EBV-driven transient lymphoproliferative disease (TLD) and diffuse large B cell lymphoma (DLBCL). XABLD is a surrogate model to study EBV-driven PTLD and DLBCL.

Methods: Tumor models were generated from patient tissue collected under NCI Tissue Procurement Protocol (https://tcap.ncifcrf.gov) and NCI Tissue Procurement Protocol (https://programs.fnlcrcr.com) for development of models for NCI’s Patient-Derived Models Repository (https://pdmr.cancer.gov). Specimens were implanted subcutaneously in NSG/SCID/IL2Rγnull (NSG) mice and animal welfare was monitored throughout the study. Tumors in mice with suspected XABLD were harvested and reviewed by histology and immunohistochemical analysis for CD4, CD8, T cell markers, EBV status, B cell clonality assay. All samples were also classified by the lymphoma handling cell of origin assay and transcrisis profiling.

Results: XABLD cases were found to originate from both solid tumor and circulating tumor cell implants. XABLD is a rapidly growing tumor positive for CD45, CD20, and EBV stain. All 42 cases are strongly positive for PD-L1 stain. 39 of 42 cases exhibited an activated B cell (ABC) phenotype with evidence of elevated NF-kB signaling. Most cases were monoclonal for IGH/IGH D and contained high numbers of tumor infiltrating CD8-positive T-cells with associated high mRNA expression of activated T cell markers.

Conclusions: The clinical presentation, morphology and molecular characteristics of XABLD cases are similar to EBV driven DLBCL. As the XABLD models exhibit increased FDG-PET expression and marked infiltration of CD8-positive T-cells, they may be useful for in vitro evaluation of checkpoint inhibitor response and T cell anti-tumor activity.

XABLD prevalence in the NCI Patient-Derived Model Repository (PDMR)

Distribution of lymphoproliferative and autoimmune cases (n=161)

<table>
<thead>
<tr>
<th>Lymphoproliferative disease occurrence by passage:</th>
<th>XABLD (n=3)</th>
<th>Murine lymphoma (n=51)</th>
<th>Human XABLD (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC</td>
<td>10</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>biopsy/resection</td>
<td>73</td>
<td>248</td>
<td></td>
</tr>
</tbody>
</table>

Sample type: ‘GvHD (n=5)’

Mixed dx in patient: solid tumor + lymphoma (n=2)

B cell lymphoma dx in patient (n=2)

In Vivo PDX Models - XABLD/Human Lymphoma Status by PDM Assigned Body Location

XABLD cases with ABC-subtype DLBCL

1. SNE plot: RNA-seq data of XABLD cases (n=26)

2. Gene expression clustering of XABLD, DLBCL and selected solid tumor histologies from the public PDMR collection

XABLD models exhibit elevated NF-kB pathway activity

• EBV+ DLBCL are known to have elevated NF-kB signaling

• Single-sample GSEA enrichment scores for 24 NF-kB target genes

Future work

• Further characterized XABLD for:
  • IGH and IGK B cell clonality assay
  • EBV latency type

• Compare gene expression profile of XABLD to DLBCL

• Characterize mutations and aneuploidy by whole exome sequencing

• Generate XABLD cell line models

• Compare treatment response of XABLD and DLBCL models

References


5. Ok CY, Li L, Saya Morimoto M, Tanaka T, Tanaka H, Marquardt GC, Monzon-Alvarez S, Dybbak K, Chiu S, Miyahara Y, Ponzoni M, Ferreri AJ, Farnen JP, Møller MB, Bueso-Ramos CE, Miranda RN, Winter JN, Piris MA, Menon MP, Jaffe ES. Additional EBV+ DLBCL gene expression datasets will be obtained to confirm that XABLD transcriptomes are similar to EBV+ DLBCL.