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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Integrative Genomic and Transcriptomic Analysis Reveals Targetable Vulnerabilities in Angioimmunoblastic T-Cell Lymphoma

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Follicular helper T-cell lymphoma of the angioimmunoblastic type (AITL) is associated with dismal prognosis. We performed functional genomic approaches including whole-exome sequencing (WES; n=119), transcriptomic (n=78) and methylation (n=40) analysis. We identified recurrent mutations in known epigenetic drivers (*TET2, DNMT3A, IDH2* ^{R172}), and also identified novel ones (TET3, KMT2D). Somatic mutation of all three epigenetic drivers (*TET2*, *IDH2*, and *DNMT3A*) was associated

with poor prognosis (p<.001). Mutations in genes regulating T-cell receptor (TCR) signaling (*CD28 VAV1*, *FYN*, *PLCG1*) or activation (*RHOA* ^{G17V}), and regulators of the PI3K pathway (PIK(3)C members, *PTEN,PHLPP-1/-2*) were also found. Genome-wide DNA-methylation analysis integrated with mRNA expression profiling also revealed epigenetic alterations in genes regulating TCR-RHOA/B/C or PI3K-signaling. TET2 loss was noted in 85% AITLs and was significantly associated with *RHOA* ^{G17V}, *CD28* and *IDH2* ^{R172}mutations. AITLs lacking *RHOA* ^{G17V} tended to have mutations regulating the JAK-STAT pathway (*JAK2*, *JAK3*, *STAT1*, *STAT3*, *SOCS1*). RNA-seq analysis identified fusion transcripts in genes regulating TCR activation (8%), revealed a restricted TCR repertoire in the majority of cases (a=87%, b=72%), and showed the presence of Epstein-Barr virus transcriptome (73%). GEP demonstrated association of B-cells in the tumor-milieu with better prognosis (p=.006), while dendritic cells were associated with worse prognosis (p=.001), which was further validated by immunohistochemistry using CD20, CD68, and CD163 antibodies. RNA-seq and corresponding WES analysis of 12 AITL patient-derived-xenografts (PDX) showed that bi-allelic *TET2* mutations, *DNMT3A* mutations or sub-clonal mutations (*PLCG1 PHLPP2) were*epropagated in sequential passages. Gene signatures related to T_{FH} (follicular helper) and T_{CM} (central memory) were also well-maintained in secondary passages in PDX models. Gene signatures of late PDX passages (3^{rd}-5^{th}) were enriched with genes related to proliferation and metabolic reprogramming, and in an independent cohort of AITLs, high expression of T3/T5 related signatures was associated with worse outcome (p=0.02/p=0.009). Low mRNA expression of PHLPP2 predicted poor prognosis (p=.03) and engineered PHLPP2 loss showed enhanced PI(3)K activation and FOXO1 inactivation in CD4+ T-cells *in-vitro*. Thus, we defined the genomic landscape for AITL, which is largely characterized by epigenetic alterations, TCR signaling and PI3K/AKT dysregulation, which may be amenable for therapeutic targeting.

Disclosures Holte: *Nordic Nanovector:* Other: Safety Committee; *Pierre Fabre:* Other: Advisory Board; *Genmab:* Other: DMC Committee; *Incyte:* Other: Advisory Board, Review Committee. **de Leval:** *Lunaphore:* Consultancy; *Novartis:* Consultancy; *Bio Ascend:* Consultancy; *Bayer:* Consultancy; *Abb Vie:* Consultancy. **Pileri:** *CELGENE:* Other: Advisory board; *ROCHE:* Speakers Bureau; *NANOSTRING:* Other: Advisory Board; *Stemline:* Speakers Bureau; *Diatech Pharmacogenetics:* Consultancy; *Beigene:* Research Funding, Speakers Bureau; *Eli Lilly:* Speakers Bureau. **Vose:** *Eli Lilly and Company; Epizyme, Kite, Loxo, Novartis:* Research Funding; *AbbVie, MEI Pharma:* Consultancy. **Dave:** *Data Driven Bioscience:* Current equity holder in private company.

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