Abstract #21 | Poster

# IRF2BP2: A novel tumor suppressor in diffuse large B-cell lymphoma

**A. Tabatabai**[1], M. Möllmann[1], M. Hartnack[1], G. Knittel[1], C. Reinhardt[1]

[1] *University Hospital Essen, Essen, Germany*

Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults and is highly heterogeneous. Traditionally classified into activated B cell-like (ABC) and germinal center B cell-like (GCB) subtypes by cell-of-origin, DLBCL has been further subdivided into molecular clusters (A53, ST2, N1, BN2, EZB, and MCD) based on mutational profiling. Although frontline chemo-immunotherapy cures ~65% of patients, relapsed or refractory disease remains difficult to treat, particularly in ABC-DLBCL and MCD subtypes.

The transcriptional repressor *IRF2BP2* is frequently mutated in MCD patients, with most variants predicted to cause loss-of-function. Consistent with human data, *Irf2bp2* is among the most commonly co-mutated genes in MCD mouse models. However, its functional role in lymphoma pathogenesis remains unclear.

To define IRF2BP2-dependent regulatory networks, we performed IRF2BP2 and H3K27Ac ChIP-seq together with ATAC-seq in human ABC/MCD-DLBCL cell lines. IRF2BP2 binding sites were strongly enriched for IRF motifs and showed differential H3K27Ac and chromatin accessibility signals. These motifs are frequently located near cytokine genes involved in inflammatory responses. Multiplex cytokine profiling demonstrated significantly increased secretion of inflammatory cytokines, including IL-1β, in IRF2BP2 knockout cells, which was confirmed by ELISA.

Despite increased IL-1β protein secretion, IL1B mRNA levels were unchanged, suggesting differential cleavage of IL-1β. Indeed, IRF2BP2-deficient cells showed enhanced caspase-1 activation, promoting cleavage of pro-IL-1β into its active form. In addition, IRF2BP2 binds regulatory regions of multiple inflammasome-related genes, including ZBP1, TET2, STK24, and RPTOR, which exhibit altered H3K27Ac after IRF2BP2 loss.

Functionally, CRISPR/Cas9-mediated IRF2BP2 knockout in ABC/MCD-DLBCL cells resulted in increased proliferation and NF-κB signaling. This IL-1β–NF-κB autocrine loop was therapeutically targetable: IRF2BP2-deficient cells were sensitive to IL-1β inhibition in vitro and in vivo, whereas IRF2BP2-proficient cells were not. Furthermore, IRF2BP2-deficient cells were also sensitive to other therapeutic targets of the inflammasome, including GSDMD, NLRP3, and mTOR.

Together, these findings identify IL-1β as a key driver of enhanced NF-κB signaling following IRF2BP2 loss and support targeting the inflammasome as a promising strategy for patients with IRF2BP2-mutant DLBCL.