Abstract #15 | Poster

# LUBAC activity is required for ABC-DLBCL pathogenesis

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Activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL) is a subclass of DLBCL associated with a high relapse rate after treatment, and a poor prognosis. At the molecular level, the pathogenesis of ABC-DLBCL is distinguished by mutations in the B-cell receptor signaling pathway resulting in chronic activation of NF-kB which is known to drive tumour proliferation and migration, significantly contributing to the poor clinical outcome.The Linear Ubiquitin Chain Assembly Complex (LUBAC) consisting of HOIL-1, SHARPIN and HOIP is the only currently known E3 ligase capable of the *de novo* synthesis of linear (M1) ubiquitin chains known to act downstream of many immune receptor signaling, including the B-cell receptor, and to regulate NF-kB signaling, cell death and inflammation. While a role for LUBAC in lymphomagenesis has been described, currently, it is unclear how LUBAC activity affects the etiology of ABC-DLBCL and importantly the molecular mechanisms that require linear ubiquitination to promote the disease. In this study we employed the MBC (*Myd88*$^{c\text{-}p.L252P/WT}$;*Rosa26*$^{LSL.BCL2.IRES.GFP/WT}$;*Cd19*$^{Cre/WT}$) mouse model and investigated the role of linear ubiquitin by modulation the catalytic activity of either HOIP or HOIL-1. We therefore generated two additional MBC models one in which HOIL1 was catalytically inactive (MBC HOIL$^{ci}$) and one in which malignant B cell were devoid of HOIP catalytical activity (MBC HOIP$^{cond.ci}$). Our work shows the importance of LUBAC activity in the pathogenesis of ABC-DLBCL lymphomas *in vivo* since HOIP activity depletion completely prevented lymphomagenesis while loss of HOIL-1 activity significantly affected the onset and the severity of the disease. Furthermore, our data show the efficacy of LUBAC targeted inhibition for the treatment of this disease as a first line - single agent and also a synergistic affect in combination with standard of care.

With our findings we are able to attribute an indispensable role for LUBAC activity downstream of the My-T-BCR-receptor aberrant signaling rendering linear ubiquitin a crucial regulator of malignant B-cell transformation and signaling activation and an important target to warrant therapeutic benefit.