Abstract #35 | Poster

IRF2BP2: A new player in diffuse large B-cell lymphoma

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Diffuse large B-cell lymphoma (DLBCL) is a highly heterogeneous disease and is the most common lymphoid malignancy in adults. It is traditionally divided into two subtypes based on the cell-of-origin: activated B-cell like (ABC) DLBCL and germinal center B-cell like (GCB) DLBCL (Alizadeh et al., 2000). DLBCL can be further subdivided into 6 clusters (A53, ST2, N1, BN2, EZB, and MCD) based on the mutational profiles of the tumors (Schmitz et al., 2018, Wright et al., 2020). While cure rates of ~60% are achievable in DLBCL patients with frontline combination therapy R-CHOP, relapsed/refractory patients have a very poor prognosis, especially in the ABC-DLBCL/MCD subtypes.

Interferon regulatory factor 2 binding protein 2 (*IRF2BP2*) is a transcriptional regulator that is frequently mutated particularly in ABC-DLBCL patients, with many of these mutations predicted to be loss-of-function. However, the role of *IRF2BP2* in lymphoma biology and as a potential tumor suppressor gene in DLBCL has not been explored in detail. Here, we show that the loss of *IRF2BP2* in human ABC-DLBCL cell lines leads to increased proliferation and NF-KB signaling, compared to *IRF2BP2*-proficient cells. Additionally, we find that *IRF2BP2* knockout ABC-DLBCL cells express higher interleukin-1 beta (IL-1B) and are sensitive to anti-IL-1B inhibition both *in vitro* and *in vivo* while *IRF2BP2*-proficient cells remain insensitive. These preliminary findings warranted an ongoing preclinical investigation of anti-IL-1B therapy in *IRF2BP2* knockout/mutant models, as well as the generation of a B-cell specific *IRF2BP2* knockout autochthonous mouse model to further characterize the role of *IRF2BP2* in lymphomagenesis.