Abstract #20 | Poster

Modulation of tumour microenvironment by BIRC3-loss-of-function in CLL

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The BIRC3 gene encodes cellular inhibitor of apoptosis (cIAP)2, which functions as an E3 ligase attaching ubiquitin chains (e.g., K63 and K48 linkages) to diverse target proteins. Despite its potent anti-apoptotic function, cIAP2 also plays a crucial role in NF-κB activation. This process delivers pro-survival signals to leukemic cells, regulating cytokine production and influencing the tumor microenvironment (TME). Mutations in *BIRC3* (the gene encoding cIAP2) are highly prevalent among patients with chronic lymphocytic leukemia (CLL). Loss of both alleles of *BIRC3* serves as an independent marker for treatment resistance, indicating the presence of high-risk patients with CLL. Therefore, elucidating the role of cIAP2 in lymphomagenesis is imperative. Our study aims to uncover the role of cIAP2 in lymphomagenesis and offer a mechanistic insight into how mutations in cIAP2 associated with lymphoma contribute to the development, progression, and therapeutic outcomes of CLL.

In our study, we generated CRISPR cIAP2-KO cell lines in RAMOS and OSU cells lines to study their intrinsic signalling events upon stimulation with different ligands and their interaction with microenvironmental cells, primarily macrophages. Furthermore, in a drug screen we discovered an interesting interaction between cIAP2 and PI3K signalling.