CCRL2 and who? An important driver in *TP53*-mutant myeloid leukemias

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Mutations in tumor suppressor gene *TP53* are associated with adverse outcomes in myeloid malignancies,[1,2] and are enriched in acute erythroleukemia.[3] *TP53*-mutant myeloid neoplasms are characterized by resistance to current therapies and higher rates of relapse.[1] Recent studies have shown that a chronic inflammatory bone marrow microenvironment may drive progression of *TP53*-mutant myeloid leukemias.[4] IFN-γ mediated JAK-STAT signaling has been implicated in progression of monocytic leukemias.[5] The mechanistic link between the role of IFN-γ signaling and TP53-mutant leukemias is not well understood.

Previous work by Karantanos *et al*. showed that the C-C motif chemokine receptor-like 2 (CCRL2), a protein involved in activation of inflammatory signaling, is significantly up-regulated in blasts from patients with myelodysplastic syndromes (MDS) compared to *de novo* acute myeloid leukemia (AML) and healthy controls.[6] Additionally, silencing of CCRL2 was sufficient to decrease MDS and AML cell growth and increase their sensitivity to azacitidine *in vitro* and *in vivo*.[7] Given the significance of CCRL2 in these contexts, the authors seek to understand if it may be of similar importance specifically in *TP53*-mutant AML with erythroid differentiation.[8]

Assessment of publicly available data showed that AML with erythroid and megakaryocytic differentiation had higher *CCRL2* expression compared to other AML subtypes in patient samples. Importantly, *TP53*-mutant AML had higher *CCRL2* expression compared to *TP53* wild-type (WT) AML. To investigate the role of CCRL2 in *TP53*-mutant AML, authors silenced CCRL2 in *TP53*-mutant AML and erythroleukemia cell lines, resulting in suppressed growth *vitro* and *in vivo*. In contrast, *TP53*-WT AML cells were not impaired by CCRL2 knockout (KO). These data suggest a functional role of CCRL2, specifically in *TP53*-mutant AML cells. To gain insights into the mechanistic link between CCRL2 and *TP53*-mutant leukemogenesis, authors pursued transcriptomic and phosphoproteomic studies comparing CCRL2 WT *versus* KO cells. Members of the IFN-γ signaling pathway were down-regulated upon CCRL2 KO. These findings are concordant with the previous work from this group, which showed that CCRL2 promotes JAK-STAT signaling.[6] The authors also developed a doxycycline-inducible CCRL2 model and found that cells treated with doxycycline exhibited increased phosphorylation of STAT1 at Y701 and S727. When treated with a JAK2 inhibitor, Y701 phosphorylation decreased and S727 remained unchanged. These findings implicate CCRL2 in STAT1 signaling, a process that is, at least in part, reliant upon JAK2.

Next, the authors compared their CCRL2 KO transcriptomic data to published datasets and they uncovered a list of 18 genes which were associated with both CCRL2 and IFN-γ signaling. These genes were then used to score different AML subsets for their expression of these genes. In both patient samples and AML cell lines, acute erythroleukemia had consistently higher expression levels than other AML subtypes. Importantly, *TP53*-mutant AML scored higher than *TP53*-WT AML and healthy controls.

Based on the data showing increased STAT1 signaling driven by CCRL2 in *TP53*-mutant AML, the authors investigated whether this pathway depends on exogenous IFN-γ stimulation. Firstly, T cells sorted from *TP53*-mutant AML patients secreted lower levels of IFN-γ when compared to controls. In addition, treatment of CCRL2 KO cells with exogenous IFN-γ did not alter the expression of IFN-γ targets when compared to controls, which suggests that CCRL2 may be required for cell intrinsic effects of IFN-γ response. In consideration also of the previous work showing down-regulated *IFNG* gene expression in patients with *TP53*-mutant AML,[5] this suggests that more work is needed to fully understand the role of exogenous IFN-γ in mediating the oncogenic effects of CCRL2 in *TP53*-mutant AML.

Patients with acute erythroleukemia and *TP53*-mutant AML often present with resistance to BH3 mimetic venetoclax.[1] The authors investigated the value of their CCRL2/IFN-γ gene expression score in predicting venetoclax response by

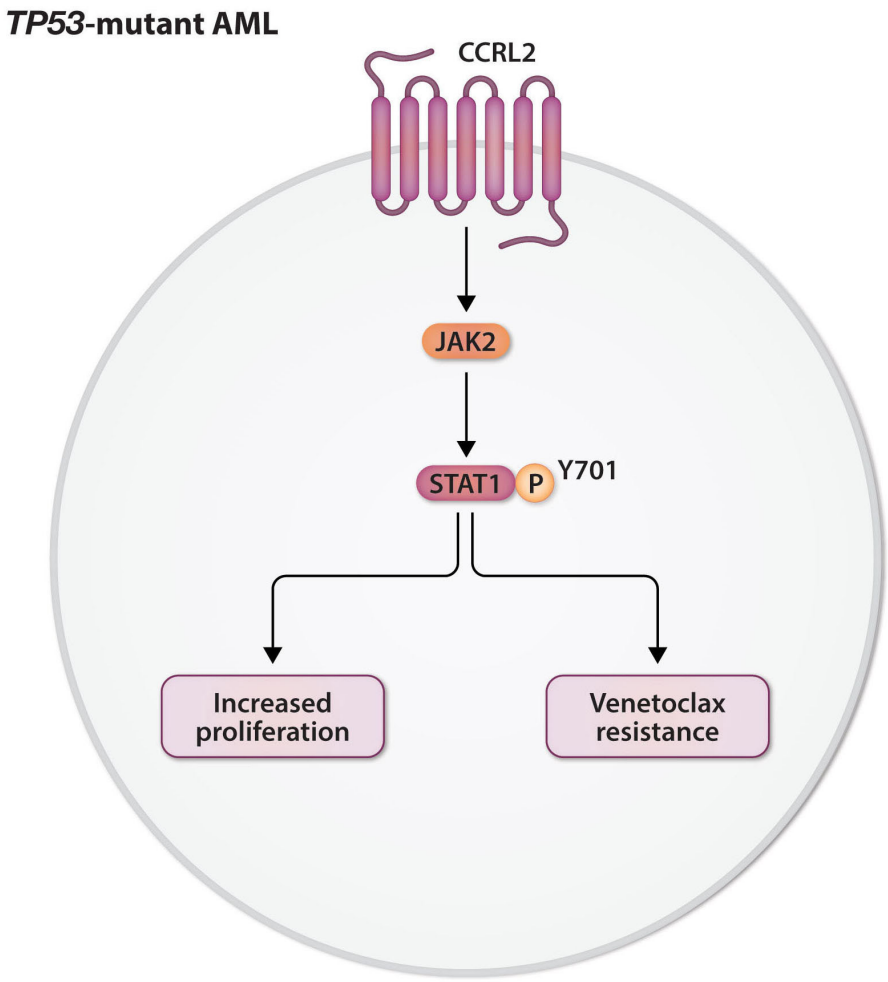

Figure 1. CCRL2 increases JAK-STAT1 signaling and drives venetoclax resistance in *TP53*-mutant acute myeloid leukemia. AML: acute myeloid leukemia.

using the Beat AML dataset. Patients with higher expression of the CCRL2/IFN-γ gene signature had higher IC_{50} values with venetoclax when compared to patients with lower gene scores. They corroborated this finding by incubating *CCRL2* KO cell lines with venetoclax and found they were more sensitive to the drug than *CCRL2* WT, implicating CCRL2 in resistance to venetoclax treatment.

In summary, Naji *et al*. highlight an important role for CCRL2 in *TP53*-mutant AML and acute erythroleukemia by establishing new mechanistic insights with CCRL2-regulated STAT signaling in high-risk subsets of AML (Figure 1). While these findings are interesting, additional experimental work is necessary to establish the link between IFN-γ, TP53 and CCRL2. It would be interesting to understand if CCRL2 is directly interacting with IFNGR, and whether the relationship between CCRL2 and downstream IFN-γ signaling is TP53-mediated. From a translational perspective, these results open up several avenues for further research. Firstly, CCRL2 may serve as a biomarker for identifying subsets of *TP53*-mutant myeloid neoplasms with heightened inflammatory signaling. Secondly, CCRL2-IFN-γ axis modulation could represent a novel therapeutic approach, particularly in a patient population with limited effective treatment options. Whether targeting CCRL2 directly, or indirectly modulating its ligands and signaling partners, can translate into clinical benefit remains to be determined.

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No conflicts of interest to disclose.

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