EDITORIAL

Putting the brakes on cyclin C: a promising strategy to cure B-cell acute lymphoblastic leukemia?

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In this issue of *Haematologica*, Trifinopoulos *et al.*[1] have identified an important role for cyclin C (CCNC) in the development and maintenance of B-cell precursor acute lymphoblastic leukemia (B-ALL). B-ALL is a clonal malignant disease characterized by rapid and uncontrolled proliferation of poorly differentiated B-lineage lymphoblasts.[2] With the advent of novel tyrosine kinase inhibitors, mono-/bi-specific antibodies and chimeric antigen receptor (CAR) T-cell therapies, pediatric-ALL is curable in 90% of the cases but these therapies fail to cure 60% of adult ALL cases.[3] Thus, a deeper understanding of the molecular mechanisms that drive B-ALL initiation, maintenance and relapse is critical for developing novel pharmacological inhibitors and innovative treatment strategies.

In this regard, Trifinopoulos *et al.*[1] skillfully leveraged the freely accessible DepMap database[4] to explore the dependency of different cancer cell types on the components of CCNC-CDK8/19 kinase complex. They discovered that the growth of B-cell lymphoblastic leukemia lines is particularly dependent on cyclin C expression, prompting further investigation into its role in leukemia. Since germline deletion of cyclin C causes embryonic lethality due to defects in placental development,[5] the authors used the hematopoietic-specific Vav-Cre system to delete *CCNC* in murine hematopoietic cells. Notably, in this setting, *CCNC* deletion did not disrupt normal hematopoiesis, consistent with previous findings in human hematopoietic stem and progenitor cells.[6]

To study the importance of *CCNC* in B-ALL initiation, Trifinopoulos *et al.*[1] transduced $CCNC^{fl/fl}$ bone marrow (BM) cells and $CCNC^{\Delta/\Delta}$ BM cells with a retroviral *BCR-ABL1* construct. They found that while $CCNC^{fl/fl}$ *BCR-ABL1* transformed cells formed colonies and engrafted mice, leading to fatal leukemia within five weeks, absence of CCNC impaired the initial leukemic transformation, as evidenced by the reduced number of colonies and low engraftment levels. The failure of *CCNC* knockout (KO) leukemia cells to elicit *BCR-ABL1* transformation was attributed to their elevated apoptosis onset. Of note, *CCNC* deficient *BCR-ABL1* expressing cells demonstrated increased propensity for cell death particularly under growth factor starvation conditions (Figure 1). These interesting results reinforce the previously proposed role of cyclin C in cellular response to metabolic stress.[7] However, while absence of cyclin C might promote cell survival under metabolic stress (via promoting growth arrest), oncogene driven hyper-proliferative signals overwhelm this conserved adaptative strategy and promote cell death. Concomitant induction of the opposing growth control signals (e.g., cell cycle exit and entrance) might expose additional synthetic lethality pathways for the *BCR-ABL* oncogene.

Transcriptomic analysis of $CCNC^{fl/fl}$ and $CCNC^{\Delta/\Delta}$ BCR-ABL transformed cells *in vitro* and *in vivo* revealed upregulation of "P53 pathway" and "apoptosis" gene sets in the KO cells, particularly *in vivo*. This indicates a complex interaction between oncogenic signaling and stress pathways that may differ between *in vitro* and *in vivo* environments. Although the reasons for the distinct transcriptional and, possibly, functional signaling remain unknown, inactivation of p53 itself or several of its pathway genes (e.g., GADD45, PLK2 and *14-3-3*σ) restored the growth and the leukemogenicity of the CCNC KO cells, implying a crucial role of P53 in this process.

And finally, Trifinopoulos *et al.*[1] have relied on genetic inactivation of CCNC in the established BCR-ABL leukemic cells to explore the theraputic prospects of cyclin C targeting. The authors transduced $CCNC^{fl/fl}$ BM cells and $CCNC^{\Delta/\Delta}$ BM cells with a retroviral BCR-ABL1 construct and used an interferon inducible MX1-Cre system to knockout *CCNC*. *CCNC deletion* severely impeded the proliferation of *BCR-ABL1* transformed mouse leukemia cells. Moreover, they demonstrated that human leukemia cell lines, regardless of Philadelphia chromosome status or p53 mutation, also depend on high levels of CCNC for growth *ex vivo*.

As is often the case, more questions remain to be answered.

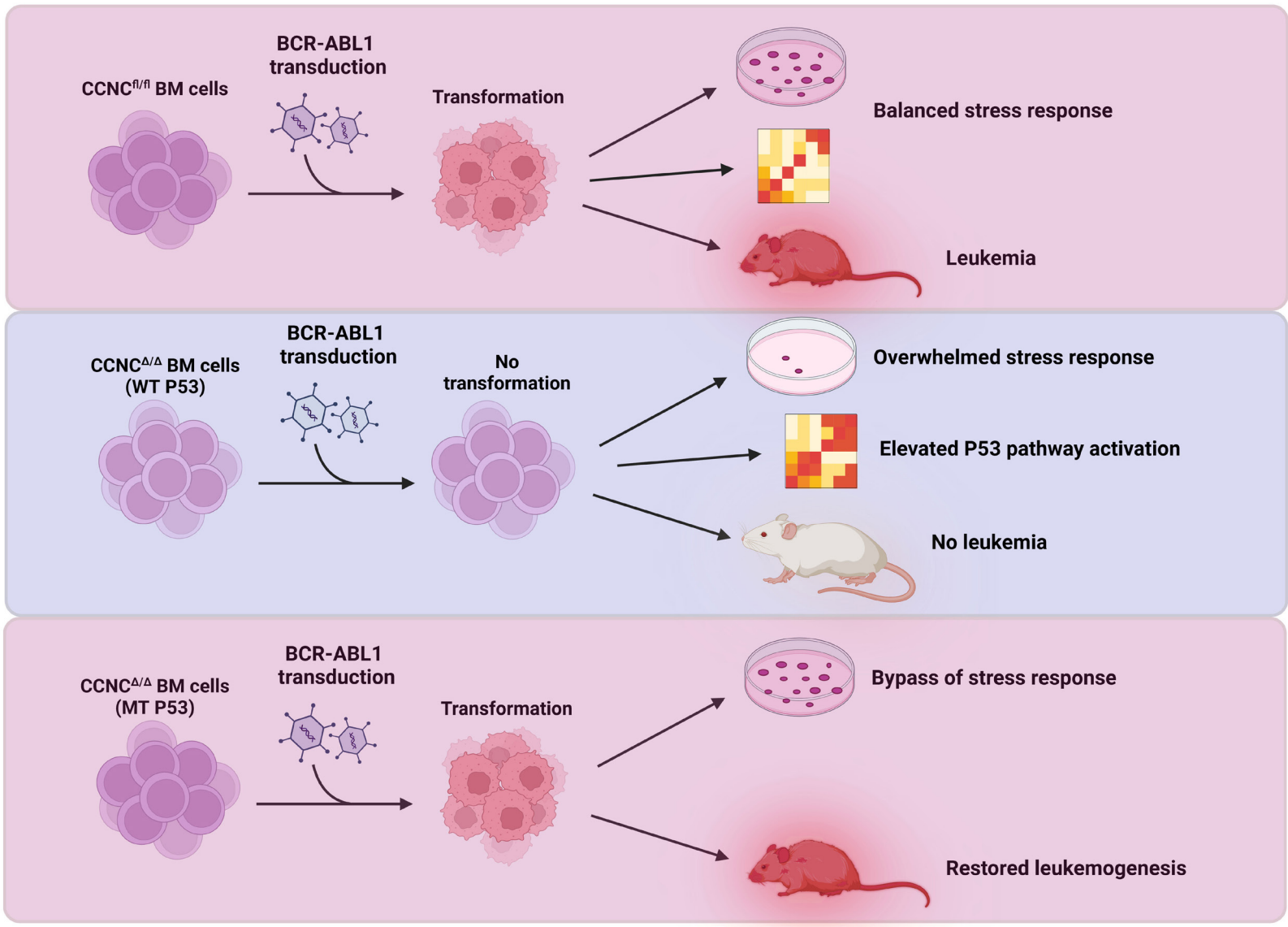

Figure 1. Schematic overview of cyclin C roles in BCR-ABL-mediated transformation and leukemia development. Cyclin C (CCNC) expression in immature bone marrow (BM) cells is essential for regulating cellular stress responses triggered by the BCR-ABL oncogene. Genetic inactivation of CCNC leads to excessive activation of the p53 tumor suppressor, resulting in the disruption of transformation and the arrest of leukemia progression. WT: wild-type.

For instance, what is the molecular and cellular basis for the "seemingly opposite" functions of cyclin C in BCR-ABL (as shown in this study) and oncogenic Notch1 (ICN1)-driven leukemias?[5] How does cyclin C communicate with p53 in the context of metabolic and oncogenic stresses? Could changes in cyclin C explain lineage plasticity occurrence during ALL initiation and upon therapy?[8] How do leukemia cells with different cyclin C levels respond to conventional and targeted therapies?

Despite these open questions, comprehensive *in vitro* and *in vivo* analysis from Trifinopoulos and colleagues nominate cyclin C as a novel theraputic target for B-ALL. While specific inhibitors of cyclin C do not yet exist, strategies such as targeted protein degradation (e.g., molecular glue degraders or PROTAC) or inhibition of its kinase partners (e.g., CDK3/CDK8/CDK19) could offer new avenues for treatment. Future research will determine whether putting the brakes on cyclin C can slow or even halt the progression of B-ALL and additional hematologic malignancies.

Disclosures

No conflicts of interest to disclose.

Contributions

SSNAM and MM wrote the manuscript.

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