Azacitidine, venetoclax and leukemia stem cell metabolism

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1. What is the most important message readers should remember from your work?
DP: This regimen presents a very hopeful treatment option for older AML patients who cannot tolerate standard intensive chemotherapy approaches. The deep and durable responses observed in a majority of patients can at least partially be explained by the ability of this therapy to target the leukemia stem cell population; the way it does this is very novel and exciting.

2. Does the therapy show an association with certain (geno-) types of AML? Why?
DP: One of the really exciting things about this regimen is that in the setting of newly diagnosed patients it appears to be as effective or nearly as effective in patients with adverse risk disease features as in those patients without those features. There may be some associations between decreased responses and some genomically-defined subtypes and we're actively investigating this now.

3. Your results indicate that the drugs selectively target LSCs over other cell types in the bone marrow. Can you elaborate on why LSCs may be selectively targeted over normal HSCs?
CJ: We reported in 2013 (Lagadinou et al., Cell Stem Cell) that LSCs preferentially rely on oxidative phosphorylation for survival. Upon treatment with regimens that inhibit this process, LSCs are eradicated. Normal HSCs appear to be less reliant on oxidative phosphorylation, and can compensate by increasing utilization of glycolysis.

4. What are your thoughts about adding additional drugs to further enhance LSC eradication? For example, one might target adaptive pathways (van Galen et al., 2018).

CJ: We think that one critical next step is to identify the subset of patients that may have a need for additional therapy and target the adaptive pathways that confer therapy resistance. Our current work demonstrates that one of these adaptive pathways may be fatty acid metabolism. We are pursuing the combination of fatty acid metabolism inhibitors with ven/aza in patient samples that we have identified as therapy resistant.

5. What is the most pertinent question that this work raises for future studies?
DP: While venetoclax-based regimens are very exciting for newly diagnosed patients, it is much less active for relapsed/refractory AML. Going forward, we are very interested in learning if patients who relapse have an LSC population that can also be targeted through metabolic vulnerabilities.

6. What was the most difficult hurdle to overcome during this work?
DP: Obtaining specimens from patients during the first few hours of therapy and performing detailed phenotypic analyses was very challenging, and required the efforts of a large highly dedicated team. We were fortunate to have wonderful colleagues/collaborators that made our work possible.

7. How did you celebrate when the paper was accepted for publication?
CJ: The work described in the two papers was truly a collaborative effort; therefore, to celebrate Dr. Jordan treated everyone in the group to a nice lunch.

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For older patients with acute myeloid leukemia (AML), a new combination therapy of azacitidine + venetoclax was recently shown to be effective and well tolerated (DiNardo et al., 2018). Recent work that came out in Cancer Cell and Nature Medicine elucidated the mechanism by which these drugs target leukemia stem cells (LSCs), that are the main

drivers of AML progression and relapse. This work was in part carried out in the laboratory of Dr. Craig Jordan, who has an impressive track record of studying the biology of LSCs (Pollyea and Jordan, 2017).

In the first study, Dr. Pollyea et al. report that the combination treatment of the BCL-2 inhibitor venetoclax and azacitidine leads to superior clinical outcomes in older patients with AML (Pollyea et al., 2018). Mechanistic analyses showed that this treatment leads to inhibition of the electron transport chain complex II, disruption of the TCA cycle, and suppression of oxidative phosphorylation (OXPHOS).

In the second study, Dr. Jones et al. add additional mechanistic insights to the mechanism by which venetoclax and azacitidine lead to LSC depletion (Jones et al., 2018). She showed that LSCs require elevated amino acid (AA) metabolism compared to non-LSCs. Venetoclax and azacitidine treatment decreases amino acid uptake, reducing OXPHOS and leading to LSC death. LSCs from relapsed AML patients have altered metabolic requirements and are less sensitive to the treatment.

Both studies convincingly demonstrate that specific metabolic requirements of LSCs can be therapeutically exploited. I interviewed first authors Courtney Jones and Daniel Pollyea about their work.

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