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AUTHOR'S VIEW

Transcriptomic profile of intrinsically chemoresistant acute myeloid leukemia patients

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ABSTRACT

We recently identified three sub-populations of refractory acute myeloid leukemia (AML) patients with distinct intrinsic resistance mechanisms. Furthermore, we were able to risk-stratify the overall survival of the patients and identify patients who would likely benefit from alternative therapies.

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Acute myeloid leukemia (AML) is driven by uncontrolled proliferation of competing oligoclonal hematopoietic progenitors. A standard initial treatment regimen for AML patients has been induction therapy, which is a combination of cytarabine and anthracycline-based chemotherapy. However, up to 30–40% of the patients will develop refractory AML with median survival of less than 1 year.[1,2] Although many advances have been made in AML treatment, we still lack a clear understanding of its biology and resistance mechanisms.

In a recent study,[3] we performed RNA-sequencing analysis of 154 pre-treated samples[4] from newly diagnosed adult AML patients. We had information on the post-treatment response of each patient. Pairwise gene expression analysis was performed on refractory patients and complete responders. We found that refractory (Ref) patients clustered into three subpopulations (Ref1, Ref2, and Ref3) with distinct gene expression and pathways (Figure 1). All Ref patients had pathways upregulated in cell replication but the highest upregulation was observed in Ref1. Pathways involved in translation were upregulated in Ref2 but downregulated in both Ref1 and Ref3. While metabolic pathways were upregulated in Ref1, they were downregulated in Ref2 and Ref3. Ref3 was predominantly enriched for downregulated pathways; however, this group overexpressed stem-cell signatures and ATP-binding cassette (ABC) transporter genes. We then utilized the gene expression signatures of Ref3 patients, who had the poorest overall survival, and identified a four-gene refractory signature (RG4), composed of glucuronidase beta (*GUSB*), aldehyde dehydrogenase 3 family member B1 (*ALDH3B1*), angiomotin (*AMOT*), and member RAS oncogene family (*RAB32*) genes that could predict overall survival of the patients. Together with the 17-gene stemness (LSC17) score,[5] we were able to generate a better overall survival predictor than the LSC17 alone.

We next analyzed the *ex vivo* drug sensitivity data of the AML patients conducted by the Beat AML working group.[4] They isolated mononuclear cells from the AML patients and exposed the cells to 122 small-molecule inhibitors. We then sorted their drug sensitivity data based on their refractory sub-populations. Among these drugs, we found that flavopiridol, a cell cycle inhibitor of cyclin dependent kinase 9 (CDK9), was predicted to be the most effective drug for targeting all Ref patients compared to the complete responders. Specifically, we found that flavopiridol was the most effective at killing mononuclear cells from the Ref1 patients. Although all refractory patients had upregulated pathways involved in replication and cell proliferation, because Ref1 had the highest upregulation, this may explain why Ref1 had the best response to flavopiridol. It is important to mention that flavopiridol is an ATP binding cassette subfamily G member 2 (*ABCG2*) substrate. This may be why it is less effective in Ref3. This information could allow us to better tailor treatment regimens for more effective treatment outcomes. Although this was an *ex vivo* study, our results suggest the potential use of flavopiridol to effectively treat refractory patients. In fact, flavopiridol is successfully being used to treat both high-risk AML patients and also those who are refractory. In addition, flavopiridol is now being tested in a clinical trial for use as part of a combination therapy. *Ex vivo* studies are able to predict patient outcome and will be useful for designing individualized treatment regimens.

We also found from our recent study that Ref3 patients had the worst overall response to most of the small-molecule inhibitors. The Ref3 subpopulation overexpressed ABC transporters. Most of the drugs we tested are substrates of those transporters, which can efflux the inhibitors from the cells. Furthermore, this group had the highest stem-cell signatures. Together, this may explain why this sub-population had the poorest overall survival compared to the other refractory groups. Targeting this sub-population will be challenging, and drugs used to treat this group should be tested to determine if they are substrates of ABC transporters.

In summary, through gene expression profiling of *de novo* AML, we were able to identify three intrinsically resistant subpopulations of AML patients. Rather than treating all refractory patients with the same treatment regimen, understanding their biology and tailoring treatments for each patient subpopulation may greatly improve overall patient survival.

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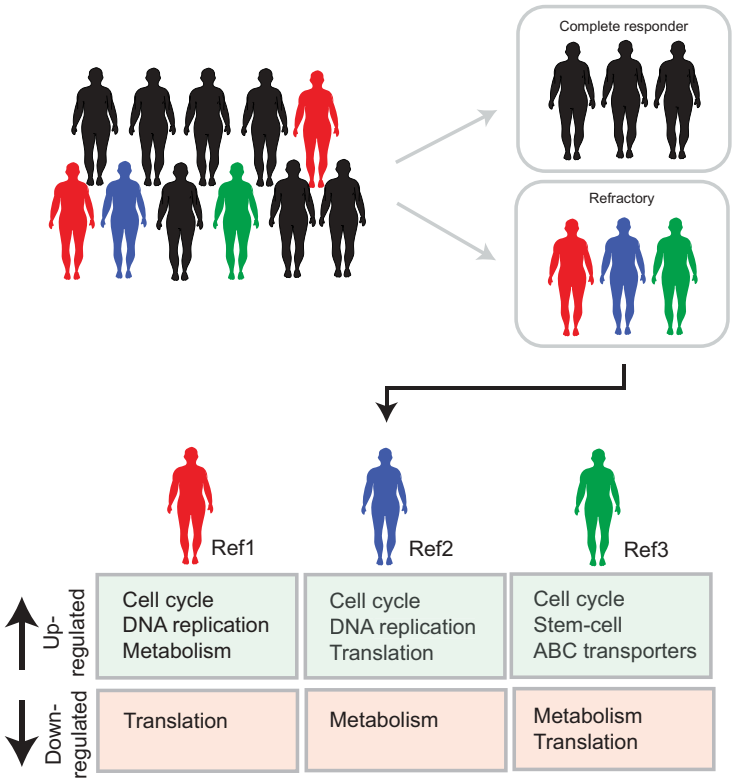

Figure 1. Intrinsically chemoresistant acute myeloid leukemia patients. There are three refractory (Ref) sub-populations (Ref1, Ref2, and Ref3) of acute myeloid leukemia (AML) patients based on their gene expression profiles. Three refractory sub-populations are indicated as Ref1 (red), Ref2 (blue), and Ref3 (green), with distinct gene expression profiles. Key upregulated and downregulated pathways in each sub-population are indicated.

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Disclosure of potential conflicts of interest

No conflict of interest.

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