Primetime for chemotherapy in acute myeloid leukemia

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The basis for the current treatment of acute myeloid leukemia (AML) was developed 40 years ago, and consists of cytarabine (a nucleoside analog) in combination with an anthracycline (DNA intercalating agents and topoisomerase II inhibitors).[1] Additional topoisomerase inhibitors are under investigation, and may help to improve the current therapies.[2] Advances in genomic technologies have identified AML as a genetically heterogeneous disease, and many patients can now be categorized into clinicopathological subgroups based on the presence of genetic defects.[3-5] On one hand, it is hoped that AML therapy can be improved through individualized treatment strategies based on molecular markers.[3-5] On the other hand, specific vulnerabilities of AML cells may be revealed by functional studies, such as RNA interference screens or chemical screens.[6-8] Letai and colleagues took yet another approach and studied the 'readiness' of AML cells to undergo apoptosis (referred to as "mitochondrial priming") as a way to understand and predict response of AML cells to chemotherapy.[9]

Mitochondrial priming is controlled by the BCL2 family of proteins, which contains both pro-apoptotic and anti-apoptotic members. The balance between these proteins determines whether a cell continues to live or activates the cell death program. Several studies have exploited the possibility to measure the 'readiness' of a cell to undergo apoptosis.[10] In practice, this is measured by the release of cytochrome c from mitochondria or the loss of mitochondrial transmembrane potential caused by pro-apoptotic peptides (BH3 peptides). While all viable cells look 'alive and kicking', mitochondrial priming studies can reveal differences in the cells' vulnerability to inducers of cell death.

In a new study, Vo and colleagues observed that mitochondrial priming of AML cell lines correlated closely with sensitivity to topoisomerase II inhibitors, such as etoposide, daunorubicin and mitoxantrone.[9] In contrast, such correlation was not observed for cytarabine, clofarabine, decitabine or azacitidine, suggesting that killing of AML cells is less dependent on mitochondrial priming by these nucleoside analogs and DNA demethylating agents. The authors next studied whether mitochondrial priming of AML blasts at diagnosis could predict the response to therapy. Interestingly, this study revealed a clear correlation between mitochondrial priming and the response of AML patients, making it possible to distinguish patients who obtained complete remission without relapse, complete remission with subsequent relapse, and those who did not obtain complete remission. Furthermore, mitochondrial priming could also further improve the prognostic information provided by molecular markers, such as those of the European LeukemiaNet (ELN).[3] These data were also in agreement with a marked difference between mitochondrial priming of sensitive AML blasts and normal hematopoietic stem cells. In contrast, AML blasts from patients who did not respond to treatment had very low priming, even lower than normal stem cells, indicating that there is no therapeutic window in these patients.

Can this resistance to treatment be reversed?

Letai and co-workers provide hope that this is indeed possible. Treatment of AML cells by ABT737, a BCL2 targeting agent, could induce apoptosis, even in low-primed AML cells, while having only little effect on normal hematopoietic stem cells.[9] With several BCL2 targeting agents currently being explored in clinical trials, it is hoped that AML treatment will be further improved in the future. While allogeneic transplantation is currently the only possible cure for poorly primed AML cases,[9] treatment with BCL2 antagonists may increase the responses to chemotherapy. Mitochondrial priming measurements can be used to identify those patients who may benefit from this therapeutic strategy. The results of this study could also be applicable to other types of leukemia, as already demonstrated in the context of chronic lymphocytic leukemia.[11]

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