Dual targeting of ALDH1 and ALDH3: A promising therapeutic approach in acute myeloid leukemia

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Background

The aldehyde dehydrogenase family (ALDHs) play a major cytotoxic role in cells via detoxification of a wide range of aldehydes. Their functional activity also extends to modulation of cell proliferation, differentiation, drug resistance, and survival of cancer cells. Despite evidences suggesting that ALDHs could be a promising target for cancer treatment, the identity of the specific isoforms contributing to this in acute myeloid leukemia (AML), the underlying mechanisms and the therapeutic value of ALDH inhibitors remain elusive.

Methods

We conducted a meta-analysis to investigate the impact of ALDHs on clinicopathological parameters and survival in AML patients. In an independent cohort (N=110), the expression of ALDHs and their corresponding enzymatic activities were monitored in AML patient-derived cells and pharmacologically inhibited with DIMATE, an irreversible suicide inhibitor of ALDH1 and ALDH3. Targeting of ALDH was evaluated both, in vitro and in orthotopic xenograft tumor models and the molecular mechanisms associated were studied in loss-of-function experiments, luciferase reporter assays and combination-index for DIMATE-drug interactions.

Results

Genes coding for ALDHs class 1&3 are up-regulated in about 45% of AML patients collected in the TCGA database (N=200). These genes present a mutually exclusive pattern, suggesting that they may have similar functions. The high expression of these isoenzymes revealed shorter survival times in patients and strong impact on chemotherapy resistance.

The subgroup of patients within the highest levels of ALDH1 have the worse prognosis. In addition, ALDH1 activity was significantly higher in refractory patients and in the subgroup of patients with adverse prognosis, according to the ELN molecular/cytogenetic classification of 2017 (p<0.005).

In a prospective cohort (N=110), as patients underwent different cycles of classical chemotherapeutic regimen with daunorubicin (DNR) and/or Cytarabine (AraC), the remaining blasts were increasingly enriched for ALDH1 activity.

In vitro and in vivo studies

Whether the increasing enrichment of ALDH-high blasts in treated patients is due to the initial existence of drug-resistant, ALDH-high clones or the adaptive response to the drug-selective pressure remains to be clarify.

Using commercially available AML cells lines we found that three specific isoforms of the ALDH class 1 & 3 subfamilies are upregulated following in vitro treatment with cytarabine (Ara-C) or daunorubicin (DNR).

Higher cytotoxic effect of the ALDH1&3 inhibitor DIMATE in AML blast vs normal haematopoietic CD34+ cells

Antitumor effect of DIMATE in xenograft mice, generated from CD34+ leukemic cells.

Intraperitoneal administration of DIMATE (3twk) induced a significant depletion of human leukemic cells in peripheral blood, as well as in bone marrow and spleen organs in all the animals receiving the doses of 28mg/kg of the drug.

Conclusion

Our data provide a proof of concept that AML with increased expression of ALDH1 and 3 may benefit from strategies including inhibitors of these isoenzymes, as single agents or in combination with chemotherapy to overcome patient-specific drug resistance. For these patients, who often have poor responses and no alternative therapeutic plan, DIMATE could be a promising option.

Bibliography

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