Identification, kinetic and structural characterization of small molecule inhibitors of aldehyde dehydrogenase 3a1 (Aldh3a1) as an adjuvant therapy for reversing cancer chemo-resistance

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Abstract:

ALDH isoenzymes are known to impact the sensitivity of certain neoplastic cells toward cyclophosphamides and its analogs. Despite its bone marrow toxicity, cyclophos-phamide is still used to treat various recalcitrant forms of cancer. When activated, cyclo-phosphamide forms aldophosphamide that can spontaneously form the toxic phospho-ramide mustard, an alkylating agent unless detoxified by ALDH isozymes to the carbox-yphosphamide metabolite. Prior work has demonstrated that the ALDH1A1 and ALDH3A1 isoenzymes can convert aldophosphamide to carboxyphosphamide. This has also been verified by over expression and siRNA knockdown studies. Selective small molecule inhibitors for these ALDH isoenzymes are not currently available. We hypothe-sized that novel and selective small molecule inhibitors of ALDH3A1 would enhance cancer cells' sensitivity toward cyclophosphamide. If successful, this approach can widen the therapeutic treatment window for cyclophosphamides; permitting lower effective dos-ing regimens with reduced toxicity. An esterase based absorbance assay was optimized in a high throughput setting and 101, 000 compounds were screened and two new selective inhibitors for ALDH3A1, which have IC50 values of 0.2 µM (CB7) and 16 µM (CB29) were discovered. These two compounds compete for aldehyde binding, which was vali-dated both by kinetic and crystallographic studies. Structure activity relationship dataset has helped us determine the basis of potency and selectivity of these compounds towards ALDH3A1 activity. Our data is further supported by mafosfamide (an analog of cyclo-phosphamide) chemosensitivity data, performed on lung adenocarcinoma (A549) and gli-oblastoma (SF767) cell lines. Overall, I have identified two compounds, which inhibit ALDH3A1' s dehydrogenase activity selectively and increases sensitization of ALDH3A1 positive cells to aldophosphamide and its analogs. This may have the potential in improving chemotherapeutic efficacy of cyclophosphamide as well as to help us understand better the role of ALDH3A1 in cells. Future work will focus on testing these compounds on other cancer cell lines that involve ALDH3A1 expression as a mode of chemoresistance.

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