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Aldehyde dehydrogenases as target for biomarker and drug discovery

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Abstract

ALDHs (aldehyde dehydrogenases) are enzymes that help the body metabolise highly reactive aldehydes into carboxylic acids. ALDH deregulation has been linked to a variety of malignancies. They're useful as a cancer stem cell (CSC) marker because of the high activity found in CSCs, and high expression has been linked to chemotherapeutic drug resistance. Although the exact role of ALDH is unknown, new evidence suggests that many isoforms of the ALDH1 family, including ALDH3A1 and ALDH7A1, play important roles in a variety of cancers. We will present new data on small molecules that inhibit ALDH functional activity using cell free and cell-based assays to investigate the role of ALDH functional activity. Diethylbenzaldehyde (DEAB) was used as a control for inhibition, while the Aldefluor assay was used to demonstrate functional activity. In addition, our research in prostate cancer demonstrated that many ALDH-affinic probe compounds were effective to diminish cell survival in both drug-resistant PC3 prostate cancer cells and patient-derived samples, with a synergistic impact when combined with docetaxel. Our early drug discovery method, which includes drug design to target ALDH7A1, an enzyme connected to oxidative stress, lysine metabolism, and a variety of illnesses, including cancer, will be discussed at the symposium.

The aldehyde dehydrogenase (ALDH) family is an intracellular enzyme superfamily that oxidises a wide range of physiologically and pathophysiologically important aldehydes to harmless carboxylic acidsALDH family members not only have cytoprotective biological roles by detoxifying aldehydes, but they also influence cell proliferation, differentiation, and survival.

ALDHs are versatile enzymes that oxidise a wide variety of endogenous and exogenous aldehydes. In 31 percent of nonsmall cell lung tumours, we found genetic abnormalities in ALDH1A1, ALDH1A3, or ALDH3A1, 86 percent of which were gene amplification or mRNA upregulation, based on data from The Cancer Genome Atlas and Gene Expression Omnibus (NSCLCs). Chemoresistance was influenced by the expression of these isoenzymes, and patients' life periods were shortened. These enzymes, we thought, give an oxidative advantage for NSCLC persistence. To explore this notion, we used DIMATE, an irreversible ALDH1/3 inhibitor, in combination with genetic and pharmacological techniques. DIMATE showed cytotoxicity in 73 percent of NSCLC cell lines examined and antitumor activity in orthotopic xenografts via formation of hydroxynonenal-protein adducts, GSTO1-mediated glutathione depletion, and elevated H2O2. ALDH1/3 disruption caused cell death when combined with ROS-inducing drugs or glutathione production inhibitors, confirming this finding. Combination treatment with DIMATE produced robust synergistic effects with tumour regression in lung cancer xenografts with high to moderate cisplatin resistance. These findings suggest that NSCLCs with high levels of ALDH1A1, ALDH1A3, or ALDH3A1 could be treated with inhibitors of these isoenzymes as monotherapy or in conjunction with chemotherapy to overcome patient-specific treatment resistance.

By examining RNA sequencing (RNAseq) data in datasets from The Cancer Genome Atlas (TCGA), we first looked for changes in the expression of ALDH family genes in the two primary histopathological subtypes of NSCLC, lung adenocarcinoma (ADC) and squamous cell carcinoma (SCC) (cBioPortal). We discovered that 13% of ADC (N = 515) and 18% of SCC (N = 504) patients had transcriptional changes in ALDH1A1, ALDH1A3, or ALDH3A1 that were mutually exclusive, implying that these genes have similar functional effects. Overall, of the 158 NSCLC patients carrying alterations in any of these ALDH isoenzymes, 86% harbored either gene amplification or mRNA upregulation. The transcriptional changes seen in these isoenzymes correspond to the protein-level variations seen in normal vs. tumour tissue, with undetectable or low staining in normal pneumocytes moving to moderate or high staining in tumour tissues.

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