口頭発表

[3T14m]タンパク質-III

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[3T14m-11(P-171)]Co-crystal structure analysis of Ferulenol derivatives in complex with human dihydroorotate dehydrogenase: a therapeutic target for cancer cells living under tumor microenvironment

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Human dihydroorotate dehydrogenase (HsDHODH) is a key enzyme of the de novo pyrimidine biosynthesis pathway that catalyzes the oxidation of dihydroorotate to orotate with concomitant reduction of respiratory quinone to quinol, thus, linked to mitochondrial respiration. This pathway provides the essential pyrimidine bases required for cellular processes. The de novo pyrimidine biosynthesis is critical for tumor cells living under hypoxia and conditions of low nutrients availability. Quantification of intra- and extracellular succinate concentrations in cancer cells indicates that HsDHODH plays an additional role in the mitochondrial metabolic adaptation that occurs under tumor microenvironment conditions which is characterized by the switch of electron flow from the classical oxygen respiration to fumarate respiration.We have recently found that the natural product ferulenol is a potent inhibitor of recombinant HsDHODH exhibiting an IC50 of 132.1 nM. Furthermore, it shows selective and potent inhibition on DLD-1 cell line with an IC50 of 151 nM under tumor microenvironment-mimicking conditions. Moreover, we synthesized several derivatives of ferulenol, performed structure-activity relationship (SAR) and co-crystal structures. Co-crystal structures analysis demonstrated that ferulenol derivatives bind to the ubiquinone binding site and show diverse binding modes according to the side chain structures. These findings indicate that ferulenol has the potential for further drug design and may contribute to the development of novel and potent anti-cancer therapies.